Tetrahedron Letters 53 (2012) 5769–5772

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Chemo- and regioselective modification of adenosine with tertiary cyanopropargylic alcohols

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ARTICLE INFO

Article history:
Received 6 April 2012
Revised 25 July 2012
Accepted 15 August 2012
Available online 23 August 2012

Keywords:
Adenosine
Tertiary cyanopropargylic alcohols
Adenosine cyclic ketals
Nucleophilic addition
Cyclization

ABSTRACT

Adenosine reacts with tertiary cyanopropargylic alcohols under mild conditions (K_2CO_3, DMF, 20–25 °C, 4–30 h) with 100% chemo- and regioselectivity by the way of two vicinal hydroxy groups of the ribose moiety to afford (in 52–72% yield) a novel family of adenosine cyclic ketals possessing cyano and hydroxyalkyl functions.

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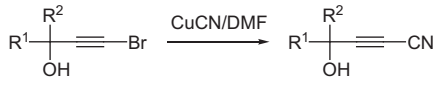
Adenosine is an important neuromodulator with both excitatory and inhibitory activities, and its extracellular concentration in the mammalian brain ranges from nanomolar to micromolar levels. Adenosine is involved in locomotion, sleep, and respiration, as well as neuroprotection during hypoxia and ischemia.[1–3] Derivatives of adenosine include important medicines such as puromycin, which represents a classic aminonucleoside antibiotic with activity against malign organisms and tumors.[2] Many other adenosine analogs and derivatives exhibit a wide spectrum of biological activity: bacterial growth inhibition,[2] anticancer,[3] cytostatic,[4,5] anti-DNA viral,[4,5] and antitrypanosomal.[6] The application of strongly fluorescent adenosine analogs as cell-growth probes[7] and inhibitors of adenosine deaminase has also been reported.[8]

In earlier work, only the pyrimidine ring of adenosine has been modified by reaction with electron-deficient acetylenes.[9] Representatives of these acetylenes such as ethyl propiolate, dimethyl acetylenedicarboxylate, and methyl (ethyl, *p*-nitrophenyl) 4-chloro-2-butynoate were shown to react with the pyrimidine moiety of adenosine, with both the triple bond and the ester group being involved in pyrimidone ring construction with participation of the amino group and pyrimidine nitrogen atom. Cyanoacetylene has been attached to adenosine 5′-monophosphate [*n*-Bu_3N, $HgCl_2$, *t*-BuOH-H_2O, 0 °C, 5 days] through the nitrogen atoms of the pyrimidine ring to furnish a new type of strongly fluorescent heterocyclic nucleotide,[10] with both the triple bond and the cyano function being utilized.

In this Letter, we aimed to develop a new approach for the modification of adenosine **1** using functionalized electron-deficient acetylenes, namely tertiary cyanopropargylic alcohols **2**. These multi-faceted, highly reactive building blocks for target-oriented organic synthesis are widely explored in heterocyclic chemistry.[11] They are readily available via the non-catalytic cross-coupling between bromopropargylic alcohols and copper(I) cyanide (Scheme 1).[12]



2a-c

$R^1 = R^2 = Me$ (**a**); $R^1 = Me$, $R^2 = Et$ (**b**); R^1-$R^2 = (CH_2)_5$ (**c**)

Scheme 1. Synthesis of tertiary cyanopropargylic alcohols **2**.

In the light of previous studies,[11a–c,g,13] it might be anticipated that adenosine **1** would first attack the triple bond of acetylenes **2** via one of its nitrogen-centered nucleophilic sites. However, competition between nitrogen- and oxygen-centered nucleophilic sites occurred in favor of the hydroxy group of the ribose moiety with 100% chemo- and regioselecitivity. Indeed, the hydroxy groups at positions 2′ and 3′ added to the same, most electron-deficient carbon atom of the triple bond to form a 1,3-dioxolane ring giving adenosine derivatives **3a–c** modified at the ribose moiety with two pharmaceutically and synthetically important functionalities (hydroxy and cyano).

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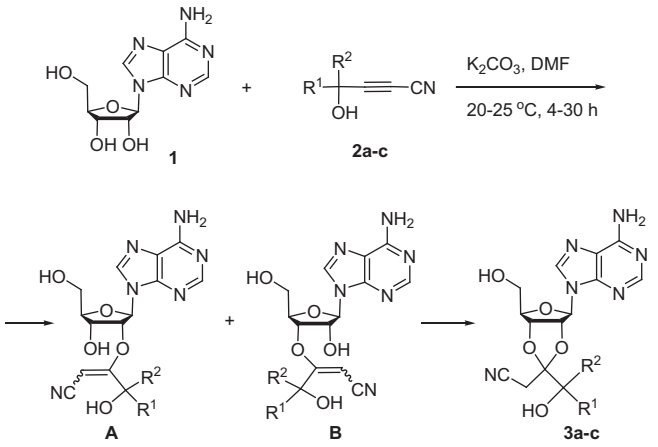
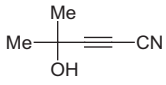
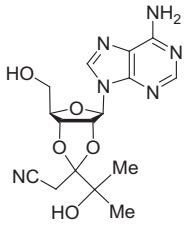
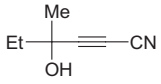
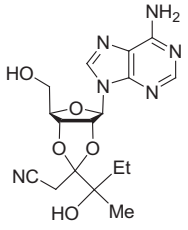
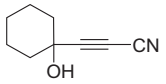
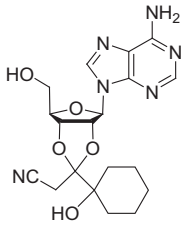
0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.08.064

The reaction proceeded smoothly when the substrates (**1**:**2** molar ratio = 1:1–1.1) were allowed to react in DMF at 20–25 °C in the presence of 50 mol % of K_2CO_3. The isolated yields of the modified adenosine derivatives **3a**–**c** ranged from 52% to 72% (based on the adenosine consumed).[14] The products **3a**–**c** exist as mixtures of two diastereomers, with one strongly prevailing, and their ratio being dependent on the structure of the starting acetylenes **2a**–**c** (Table 1). The diastereomer ratios were determined from the intensities of the proton signals in the ^{1}H NMR spectra (DMF and DMSO), and were not dependent on the solvent. As the NMR NOESY experiments turned out to be uninformative for the determination of the *endo* versus *exo* selectivity, the NMR ROESY technique was applied for product **3b**. In the NMR ROESY spectra, cross peaks between the protons of the –H_2C–CN group and proton H-4′ of the ribose moiety of the major diastereomer were observed, thus indicating the *endo* isomer to be the major product of the reaction. For adduct **3b**, additional doublings of the NMR signals were observed due to the presence of another asymmetric carbon atom (one would expect 4 isomers here, but their signals seemed to be overlapped, if indeed they were formed). The diastereomer issue, although interesting, is complicated and will be investigated in a separate publication.

In this case, despite the literature experimental data that tertiary cyanopropargylic alcohols **2a**–**c** are specifically reactive toward

Table 1
Synthesis of 2-[4-(6-amino-9*H*-purin-9-yl)-6-(hydroxymethyl)-2-(1-hydroxy-1-alkyl)tetrahydrofuro[3,4-*d*][1,3]dioxol-2-yl]acetonitriles **3a-c**



Acetylene	Product	Conversion of **1** (%)	Yield of **3**[a] (%)	Ratio of diastereomers
 **2a**	 **3a**	83	53	1:10
 **2b**	 **3b**	78	72	1:5[b]
 **2c**	 **3c**	100	52	1:8

[a] Isolated yield after preparative column chromatography (based on consumed adenosine **1**).
[b] Additional doublings of NMR signals due to the presence of other diastereomers were detected.

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