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Chemo-, regio- and stereospecific addition of adenine and 8-azaadenine to α,β-acetylenic γ-hydroxy nitriles: a short-cut to novel acyclic adenosine analogues

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ABSTRACT

Adenine (9*H*-purin-6-amine) adds readily to available α,β-acetylenic γ-hydroxy nitriles under mild conditions (molar ratio 1:1, K_2CO_3, DMF, rt, 10 min) to afford chemo-, regio- and stereospecifically *(Z)*-3-(6-amino-9*H*-purin-9-yl)-4-hydroxy-4-alkyl-2-alkenenitriles, novel functionalized acyclic nucleoside analogues (95–98% yield). Under similar conditions (K_2CO_3, DMF, rt, 1 h), 8-azaadenine (3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-amine) reacts with 4-hydroxy-4-methyl-2-pentynenitrile nonselectively at the 7-, 8- and 9-positions to give the corresponding adducts in a 1:10.5:9 ratio, the total yield being 81%. Chemo-, regio- and stereospecific addition of 8-azaadenine to the above α,β-acetylenic γ-hydroxy nitriles leading to (*Z*)-3-(7-amino-2*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-2-yl)-4-hydroxy-4-alkyl-2-alkenenitriles in 44–90% yield is attained when the reaction is carried out without solvent in the presence of Et_3N (30 mol %), the molar ratio of 8-azaadenine:α,β-acetylenic nitriles being 1:2.0 (rt, 12–38 h).

1. Introduction

Acyclic nucleoside analogues are currently used as antiviral agents, e.g., for the treatment of human immunodeficiency virus (HIV), hepatitis B (HBV), and herpes diseases.[1–4] They are also mentioned in the context of cancer therapy.[5] Most of their analogues represent modifications of the natural nucleosides in the heterocyclic or in the ribose moieties.[3,6] Usual structural alterations relate to the sugar ring where 2′- and 3′-hydroxyl functions are eliminated and the oxygen atom is replaced by a methylene group (carbocyclic nucleosides).[3,7,8] Also, 1,3-oxathiolanes[3,9] (instead of ribose derivatives) and their ring-opened congeners have been synthesized.[3,8] The latter, in some cases, were shown to be prospective antiviral remedies.[3,7] Among them are such important antiherpetic drugs as acyclovir[1,10] and ganciclovir,[1,11] both derivatives of guanine. Acyclic adenine analogues, namely, adefovir and tenofovir are active against HBV and HIV infections.[2] Attempts to synthesize new more potent analogues of these drugs are currently being undertaken.[2]

Special efforts have been directed toward the synthesis of α-branched representatives of acyclic analogues of adenosine, because some of them, for example, *erythro*-9-(2-hydroxy-3-nonyl)adenine and its derivatives, possess significant biologically activity.[5] Commonly, the preparation of such α-branched derivatives by direct alkylation of adenine encounters difficulties due to the competing elimination reactions or low reactivity of the alkylation agent.[5,12] The reported syntheses include up to five steps starting from adenine with total yield of the target adenosine analogues ranging 4–10%.[5]

Unsaturated acyclic adenosine congeners are convenient intermediates in the synthesis of the corresponding oligonucleotides[13] and polymeric analogues of nucleic acids.[13b,14] Their synthesis consists in relatively low-yield multistep procedures.[13–15] The introduction of electron-withdrawing substituents into the acyclic moiety of adenosine analogues was reported to be particularly difficult.[5] Much less is known about the application of acetylenic compounds in the synthesis of acyclic adenosine analogues. Some propargyl halides were reported to alkylate adenine whilst keeping the triple bond intact,[16] whereas non-stereoselective addition of adenine to diethyl acetylenedicarboxylate led to a mixture (2:1) of *E*- and *Z*-adducts in 65% yields.[17] To the best of our knowledge, this is the only example of adenine addition to the C≡C bond.

Derivatives of 8-azaadenine exhibit cytotoxic,[18] antimicrobial,[19] and mutagenic[18c] activities. On-going investigations into the chemistry of 8-azaadenine is anticipated to be a potential source of antitumor drugs.[18b] Of great importance is the free radical chemistry of these compounds, since tumor treatment involves both chemo- and radiotherapy.[18c] There are fewer examples of acyclic

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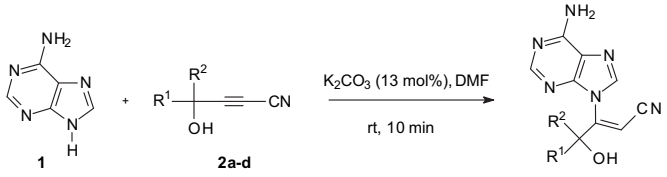
analogues of 8-azaadenine although their biological activity is predicted to be promising.

In this paper, we report an original short-cut to novel functionalized acyclic analogues of adenosine and its 8-azacongeners basing on the direct addition of adenine and 8-azaadenine to readily available α,β-acetylenic γ-hydroxy nitriles.[20]

2. Results and discussion

Various NH-heterocycles are known to react readily with α,β-acetylenic γ-hydroxy nitriles (without transition metal catalysts or in the presence of bases) to afford the expected adducts across the triple bond or their cyclic isomers, the corresponding iminodihydrofurans.[20c] These heterocycles include imidazoles (no catalyst and solvent, rt, 0.5–2 h),[20c,21] benzimidazole [Et_3N, 50 °C, 4 h or MOH (M=Na, K, Li), dioxane, 50 °C, 1 h],[20c,22] pyrazoles (no catalyst and solvent, rt, 48–72 h),[23] 1,2,4-triazoles (no catalyst and solvent, rt, 72 h)[23] and tetrazole [MOH (M=Na, K), THF (or DMSO), 20–40 °C, 13–50 h].[24] Therefore, it was a surprise that during our diversified experiments adenine **1** turned out to be reluctant to react efficiently with α,β-acetylenic γ-hydroxy nitriles **2a–d** under the conditions valid for the above heterocycles. This was likely due, at least partially, to a scarce solubility of this nucleobase in conventional organic solvents. Our systematic screening of the catalysts and conditions of the reaction allowed an efficient method of the adenine addition to the α,β-acetylenic γ-hydroxy nitriles to be developed. Eventually it was found that, when conducted at rt in DMF with K_2CO_3 (13 mol %) as catalyst, the target reaction became rapid, smooth and high-yielding (Scheme 1).



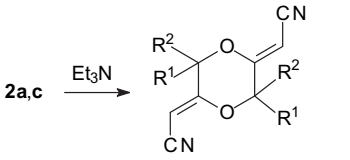
Adduct	R^1	R^2	Isolated yield (%)
3a	Me	Me	98
3b	Me	Et	95
3c			97
3d			96

Scheme 1.

Despite the presence of five nucleophilic centers (nitrogen atoms) in the molecule of adenine **1**, potentially capable of attacking the triple bond, only the imidazole nitrogen N-9 reacted with the acetylenes **2** that led to chemo-, regio- and stereospecific formation of the adducts **3a–d**, *(Z)*-3-(6-amino-9*H*-purin-9-yl)-4-hydroxy-4-alkyl-2-alkenenitriles, in 95–98% yields.

Some selected results on the screening of catalysts and conditions for the reaction under study are presented in Table 1. Among them the following features draw attention:

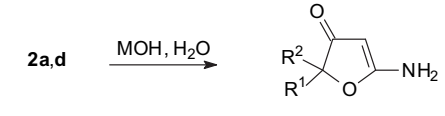
1. When carried out without catalyst and solvents (entries 1–3), the reaction is preparatively much less efficient (conversions of **1** are 15–82%, yields of **3a** are 62–72%) and takes much longer (up to four days). The comparison of conversions and yields shows that the non-catalytic reaction is not selective because some amount of adenine is used up for side processes probably for the addition to a second molecule of **2a** by its other nitrogen atoms.
2. Triethylamine as a catalyst improves preparative characteristics of the reaction increasing the conversion of adenine, yield of adducts **3** and selectivity (entries 4–7), although the reaction still is slow (from 16 h to two days) and not fully selective (cf. conversions and yields). When an excess of acetylene is employed (entries 4–7), 2,5-di(cyanomethylene)-1,4-dioxanes **4a**,**c**, the dimers of starting acetylenes **2a**,**c** previously described[25] are isolated in 16–30% yields (Scheme 2).



a: $R^1 = R^2$ = Me; **c**: R^1- R^2 =

Scheme 2.

3. Inferior results are obtained with alkaline metal hydroxides as catalysts in water or water–ethanol mixture (entries 8–10). In this case, along with adducts **3a**,**d**, 5-amino-3(2*H*)-furanones **5a**,**d** originating hydration of acetylene **2a** and **2d** as shown in[25c,26] are formed in 13–28% yields (Scheme 3).



a: $R^1 = R^2$ = Me

d: R^1 - R^2 =

M = Li, Na

Scheme 3.

Table 1
Synthesis of adducts **3a–d** [adenine **1** (1 mmol), rt]

Entry	Acetylene, mmol	Catalyst, mol %	Solvent	Time	Conversion of **1** (%)	Product	Isolated yield (%)
1	**2a**, 1.56	None	None	3 days	15	**3a**	72
2	**2a**, 2.16	None	None	2 days	55	**3a**	62
3	**2a**, 2.16	None	None	4 days	82	**3a**	68
4	**2a**, 2.20	Et_3N, 10	None	2 days	100	**3a**	81[a]
5	**2b**, 2.00	Et_3N, 45	None	18 h	79	**3b**	56
6	**2c**, 2.00	Et_3N, 50	None	26 h	100	**3c**	96[a]
7	**2d**, 2.00	Et_3N, 50	None	16 h	37	**3d**	72
8	**2a**, 1.00	NaOH, 2.5	H_2O, 3 ml	4 days	44	**3a**	47[b]
9	**2a**, 1.00	NaOH, 40	H_2O, 3 ml	24 h	74	**3a**	39[b]
10	**2d**, 1.00	LiOH, 50	EtOH–H_2O 1:2, 4.5 ml	7 h	42	**3d**	91[c]
11	**2a**, 1.00	K_2CO_3, 10	H_2O, 4 ml	24 days	—	—	—[b]

[a] 2,5-Di(cyanomethylene)-1,4-dioxanes:[25] **4a** (yield 16% for entry 4) and **4c** (yield 30% for entry 6) are isolated, yields basing on acetylenes **2a**,**c**.
[b] 5-Amino-3(2*H*)-furanone[25c,26] **5a** was formed, yield 13% – entry 8, 28% – entry 9, 80%—entry 11.
[c] 50–55 °C, 5-amino-3(2*H*)-furanone **5d** (yield 8%) was formed.

4. In water, K_2CO_3 does not catalyze the reaction at all. Instead, only hydration of starting acetylene occurs to give 5-amino-3(2*H*)-furanone **5**, for **2a** the yield reaching 80% (entry 11).

For the structure determination we have performed an X-ray analysis of a single crystal of product **3a**, which actually proves it to be (*Z*)-3-(6-amino-9*H*-purin-9-yl)-4-hydroxy-4-methyl-2-pentenenitrile **3a** (Fig. 1).

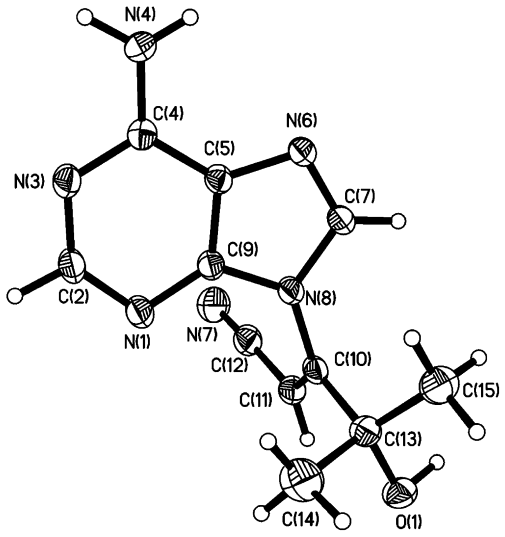


Figure 1. The conformation and designation of atoms in the adduct of **3a**.

The crystalline structure is formed by one crystallographically independent molecule taking the general position. The purine bicycle is almost planar and the maximum deviation of atoms from the plane does not exceed 0.01 Å. The deviation of N(4) and C(10) atoms from the plane is also not higher than 0.01 Å. The purine bicycle forms a dihedral angle (116.9°) with the plane of acrylonitrile N(7)C(12)C(11). The torsion angles N(8)-C(10)-C(11)-C(12), C(10)-C(11)-C(12)-N(7) and N(8)-C(10)-C(13)-O(1) are equal to 1.0(2)°, 153(5)°, and 165.1(1)°, respectively.

Multinuclear ^{1}H, ^{13}C, ^{15}N, and 2D (NOESY, HMBC, HSQC) NMR spectroscopy data as well as IR, UV, and MS investigation results of the adducts **3a**–**d** are in agreement with their structure.

In the ^{1}H NMR spectra of the adducts **3a**–**d**, there is an olefinic proton signal (H-11) at 6.56–6.53 ppm, that is, indicative of the formation of only one isomer. The *Z*-configuration of the isomers follows from 2D (^{1}H, ^{1}H) NOESY spectra where a cross-peak between the olefinic proton and the methyl group protons is observed. The configurational assignment and the substituent location for the compounds **3a**–**d** are also based on the values of vicinal coupling constant $^3J_{CH}$ between olefinic proton H-11 and carbon C-14 ($^3J_{CH}$=3.6 Hz). In the ^{15}N NMR spectra of the adducts **3a**–**d**, as exemplified by the spectrum of **3b**, four nitrogen signals of heterocyclic fragment appear at −216.4 (N-9), −154.7 (N-3), −142.9 (N-1), and −137.7 (N-7) ppm, while nitrogen signals of CN and NH_2 groups are in the region of −113.1 and −298.1 ($^1J_{NH}$=90.3 Hz) ppm, respectively.

In contrast to adenine **1**, 8-azaadenine **6** reacted with acetylene **2a** in the presence of K_2CO_3 in DMF non-selectively: all the three nitrogen atoms of the triazole moiety were involved to give the adducts **7**–**9** in the ratio 1:10.5:9 (^{1}H NMR spectroscopic data), respectively, the total yield being 81% (Scheme 4).

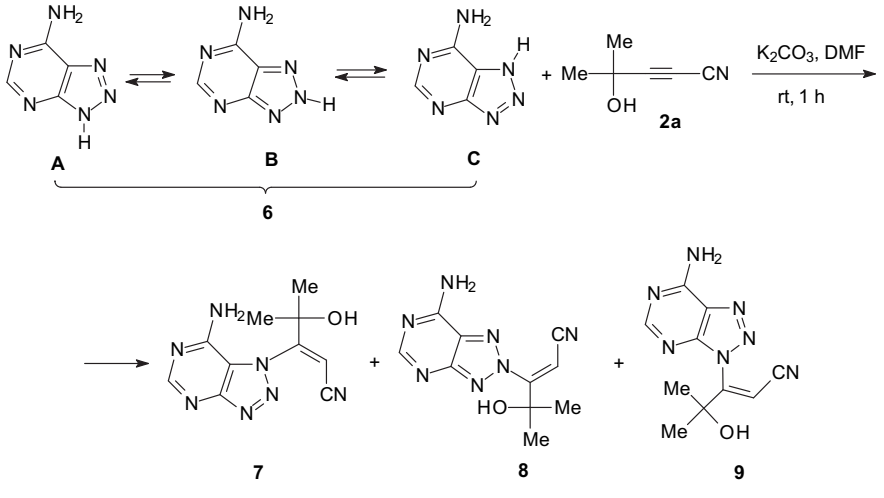
This result is in agreement with tautomeric equilibrium known for 8-azaadenine.[27]

According to quantum chemical calculations (MP2/6-31*//HF/6-31G8), the stability order for the tautomers **A**–**C** is as follows: **B**>**A**>**C**.[27] Alkylation[4a,28] of 8-azaadenine **6** leads to a mixtures of three[4a] or two[28] isomers in ratios of N-9:N-8:N-7=5:5.5:1 and 1:1.3:0. Thus, the isomer ratio obtained (Scheme 4) implies that tautomers **A**–**C** add to the triple bond of acetylenes **2** with approximately equal rates under the conditions studied.

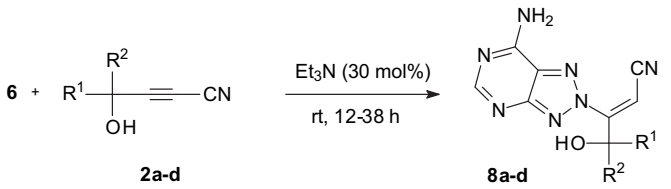
This turned out to be not the case for the reaction of 8-azaadenine **6** with a two-fold molar excess of acetylenes **2a**–**d** in the presence of Et_3N (30 mol %, rt, 12–38 h). Under these conditions, only nitrogen atom N-8 (tautomer **B**) happened to be active. As a result, chemo-, regio- and stereospecific formation of isomers **8a**–**d**, (*Z*)-3-(7-amino-2*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-2-yl)-4-hydroxy-4-alkyl-2-alkenenitriles, in 44–90% yields took place (Scheme 5).

The high selectivity of the reaction observed in this case is likely due to the tautomer reactivity change and shift of the tautomer ratio in favor of tautomer **B** (Scheme 5). The quantum chemical calculations[27] predict the electrostatic effects in solution to be important for the stability of tautomer **B**.

In the ^{1}H NMR spectra of the adducts **8a**–**d**, there is an olefinic proton signal at 6.72–6.62 ppm, that is, indicative of the formation of only one isomer. The vinyl moiety of **8a**–**d** is manifested itself in the ^{13}C NMR spectra by the signals in the region 165.8–163.3 ppm (C-10) and 100.6–98.6 ppm (C-11). The cyano C-atom resonates at



Scheme 4.



Adduct	R^1	R^2	Yieds (%)
8a	Me	Me	90
8b	Me	Et	72
8c			44
8d			52

Scheme 5.

115.4–114.8 ppm (C-12). The 2D (^{1}H, ^{1}H) NOESY spectra of the adducts **8a–d** show cross-peaks between olefinic proton and methyl group protons for compounds **8a** and **8b**, as well as between olefin proton and protons of CH_2 of the cycle substituent for compounds **8c** and **8d**.

The configurational assignment and substituent location for the compounds **8a–d** have also been based on the values of vicinal coupling constant $^3J_{CH}$ between olefinic proton H-11 and carbon C-14 ($^3J_{CH}$=3.8–3.5 Hz). Since the *trans*-vicinal $^3J_{CH}$ value is always larger than the corresponding *cis*-$^3J_{CH}$ value, the H-11 atom is located in the *cis*-position with respect to the C-14. Therefore, compounds **8a–d** are *Z*-isomers. *Z*-Stereospecificity of the additions (Schemes 1 and 5) is expected from the known *trans*-mode of concerted nucleophilic addition to acetylenes.[29]

In the 2D ^{1}H–^{15}N NMR spectra (HMBC) of compounds **8a–d**, two groups of nitrogen atom signals are observed: H-2 cross-peaks with three nitrogen atoms N-1 [δ –(147.1–146.8) ppm, $^2J_{N\text{-}H}$=16.4–16.2 Hz], N-3 [δ –(150.2–149.8) ppm, $^2J_{N\text{-}H}$=15.4–15.0 Hz], and N-9 [δ –(64.6–64.3) ppm], as well as olefinic proton cross-peaks both with nitrogen atom of cyano group [δ –(111.7–111.5) ppm] and N-8 atom of the triazole ring [δ –(122.4–122.2) ppm].

3. Conclusions

In summary, an original approach to the chemo-, regio- and stereospecific modification of adenine and 8-azaadenine has been developed. The approach consists in the nucleophilic addition of adenine and 8-azaadenine to readily available α,β-acetylenic γ-hydroxy nitriles in a one-pot procedure at room temperature to afford (*Z*)-3-(6-amino-9*H*-purin-9-yl)-4-hydroxy-4-alkyl-2-alkenenitriles **3a–d** and (*Z*)-3-(7-amino-2*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-2-yl)-4-hydroxy-4-alkyl-2-alkenenitriles **8a–d** in high yields. The methodology allows the synthesis of novel families of acyclic nucleosides with biologically important functionalities (cyano, hydroxy, and vinyl groups). Such acyclic nucleosides are potential pharmaceuticals and promising building blocks for drug design.

4. Experimental

4.1. General

^{1}H, ^{13}C and ^{15}N NMR spectra of the studied compounds were recorded in DMSO-d_6 at rt on Bruker DPX-400 and Bruker AV-400 spectrometers (400.13, 100.61, and 40.56 MHz, respectively). ^{1}H, ^{13}C, and ^{15}N chemical shifts (δ in ppm) were measured with accuracy of 0.01, 0.02, and 0.1 ppm, respectively, and referred to HMDS (^{1}H, ^{13}C) or nitromethane (^{15}N). ^{1}H–^{1}H, ^{1}H–^{13}C and ^{1}H–^{15}N Coupling constant (*J* in Hz) values approach to 0.1 Hz. NMR signals were assigned using 2D NMR methods (HSQC or HMBC ^{1}H–^{13}C and HMBC ^{1}H–^{15}N) and also with account data reported in Refs.[30] IR spectra were measured on a Bruker IFS-25 in KBr pellets. UV–vis spectra were measured on a Perkin–Elmer Lambda 35 spectrometer at rt (H_2O, EtOH, *d*=0.1, 0.3, 1.0 cm). Mass spectra were recorded on a GC–MS-QP5050A spectrometer made by Shimadzu Company. Chromatographic column parameters were as follows: SPB™-5, length 60 m, internal diameter 0.25 mm, thickness of stationary phase film 0.25 μm; injector temperature 250 °C, gas carrier—helium, flow rate 0.7 mL/min; detector temperature 250 °C; mass analyzer: quadrupole, electron ionization, electron energy: 70 eV, ion source temperature 200 °C; mass range 34–650 Da. All melting points were taken on a Kofler micro hot stage. The reaction was controlled by TLC on neutral Al_2O_3 (chloroform–benzene–ethanol, 20:4:1 as eluent). Adenine **1** and 8-azaadenine **6** are commercial reagents ('Merck'). α,β-Acetylenic γ-hydroxy nitriles **2a–d** were prepared according to a published method.[20]

4.2. X-ray diffraction

X-ray diffraction studies of **3a** were carried out with an Bruker SMART APEX2 CCD, diffractometer at rt ($\omega/2\theta$-scan mode, Mo-K_α radiation, graphite monochromator). Crystalline structure was solved by direct methods followed by Fourier synthesis using SHELXS-97.[31a] The structure was refined using anisotropic full-matrix approximation for all non-hydrogen atoms with SHELXL-97.[31b] Coordinates of hydrogen atoms were defined experimentally and refined isotropically. These data are available via www.ccdc.cam.uk/contsretrieving.html (or from CCDC, 12 Union CambrigeCB2 1EZ, UK, fax: +44(0)1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number CCDC 743626.

4.2.1. Crystallographic data for ***3a****.* $C_{11}H_{12}N_6O$, *M*=244.26, monoclinic, $P2_1/n$, *a*=6.500(1) Å, *b*=13.250(3) Å, *c*=14.040(3) Å, α=90°, β=93.60(3)°, γ=90°, *U*=1206.8(4) Å^3, *Z*=4, λ=0.7107 Å, D_{calcd}=1.34 g cm^{-3}, μ=0.094 mm^{-1}, reflection observed/independent 11509/3227, 211 parameters refined, *R*=0.048 for 2264 reflections with [$F_0>4\sigma(F_0)$].

4.3. The reaction of adenine 1 with α,β-acetylenic γ-hydroxy nitriles 2a–d

Method A. To a suspension of adenine **1** (135 mg, 1.0 mmol), K_2CO_3 (18 mg, 13 mol %) in DMF (3 mL), the appropriate acetylenes **2a–d** (1.0 mmol) in DMF (1 mL) was added at rt and stirred for 10 min. The resulting mixture was passed through neutral Al_2O_3 (0.5 cm, eluent: 3 mL of DMF) and then solvent was evaporated in vacuo. The residue was washed with diethyl ether and dried in vacuo to give (*Z*)-3-(6-amino-9*H*-purin-9-yl)-4-hydroxy-4-alkyl-2-alkenenitriles **3a–d**.

Method B. A mixture of adenine **1** (135 mg, 1.0 mmol) and acetylene **2a** (170 mg, 1.56 mmol) was stirred at rt for three days. The reaction mixture was washed with diethyl ether and dried in vacuo to give 148 mg of a solid consisting of adenine **1** (115 mg, conversion 15%) and compound **3a** (26 mg, 72%) (Table 1, entry 1).

Entries 2 and 3 (Table 1) were carried out under analogous conditions, but at different molar ratio of start compounds (**1**:**2**, 1:2.16) and reaction time (two and four days).

Method C. To mixture of adenine **1** (135 mg, 1.0 mmol) and Et_3N (10 mg, 10 mol %), the acetylene **2a** (240 mg, 2.2 mmol) were added at rt and stirred for two days. The reaction mixture was sequentially washed up acetone and diethyl ether, the residue was dried in

vacuo to give compound **3a** (191 mg). The combined organic layers were evaporated in vacuo to give 182 mg of dark-red a residue. The latter was washed with ethanol (2 mL) and diethyl ether (2 mL), the resulting white powder (45 mg) consisting 6.5 mg of compound **3a** and 38.5 mg (16%) of 3,3,6,6-tetramethyl-1,4-dioxane **4a** (^{1}H NMR data). ^{1}H and ^{13}C NMR spectra correspond to literature data.[25] Total yield **3a** is 81% (Table 1, entry 4).

Under analogous conditions compounds **3b–d** were obtained from adenine **1** (1.0 mmol), appropriate acetylenes **2b–d** (2.0 mmol) and Et_3N (45–50 mol %) (Table 1, entries 5–7), but at different molar ratio of start compounds (**1**:**2**, 1:2.0) and reaction time (16–26 h).

Method D. To solution of adenine **1** (135 mg, 1.0 mmol), NaOH (1.0 mg, 2.5 mol %) in water (3 mL), the acetylene **2a** (109 mg, 1.0 mmol) was added and stirred at rt for four days. The water was removed, the residue was washed with ethanol to result adenine **1** (76 mg, conversion 44%). Ethanol was removed in vacuo to give mixture (177 mg) consisting of compound **3a** (50 mg, 47%) and 5-amino-2,2-dimethyl-3(2*H*)-furanone **5a** (17 mg, 13%) (^{1}H NMR spectroscopic data). MS, ^{1}H and ^{13}C NMR spectra correspond to literature data[25c,26] (Table 1, entry 8).

Entry 9 (Table 1) was carried out under analogous conditions, but at 40 mol % of NaOH (24 h).

Method E. Solution of adenine **1** (135 mg, 1.0 mmol), LiOH (12 mg, 50 mol %) in water (3 mL) was stirred and heated to 50–55 °C, then solution of acetylene **2d** (109 mg, 1.0 mmol) in ethanol (1.5 mL) was added. The resulting mixture was stirred at 50–55 °C for 7 h. The solvents were removed in vacuo to result 255 mg of a solid consisting of adenine **1** (78 mg, conversion 42%), compound **3d** (110 mg, 91%), and 2-amino-1-oxaspiro[4.5]dec-2-en-4-one **5d** (14 mg, 8%) (^{1}H NMR spectroscopic data). ^{1}H NMR for **5d** (400.13 MHz, DMSO-d_6) δ 4.24 (s, 1H), 1.87–1.44 (m, 10H); MS *m*/*z* (%) (EI) for **5d**: 167 (38) $[M]^+$, 126 (16), 112 (93), 99 (15), 86 (27), 81 (35), 79 (13), 69 (33), 68 (14), 67 (14), 55 (22), 54 (12), 53 (14), 44 (18), 43 (24), 42 (20), 41 (100), 40 (18), 39 (31) (Table 1, entry 10).

*4.3.1. (Z)-3-(6-Amino-9H-purin-9-yl)-4-hydroxy-4-methyl-2-pentenenitrile **3a**.* Method A: 239 mg, yield 98%; method B: 26 mg, yield 72% (Table 1, entry 1); 84 mg, yield 62% (Table 1, entry 2); 137 mg, yield 68% (Table 1, entry 3); method C: 197 mg, yield 81%; yellow crystals; mp 220–222 °C (ethanol); IR (KBr) 3432, 3321, 3264, 3157 (NH_2, OH), 3061 (C=CH), 2225 (CN), 1662, 1643, 1600 (NH_2, C=C), 1573, 1510, 1482 (C=N) cm^{-1}; ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 8.19 (s, 1H), 8.17 (s, 1H), 7.41 (s, 2H), 6.53 (s, 1H), 5.79 (s, 1H), 1.29 (s, 6H); ^{13}C NMR (100.61 MHz, DMSO-d_6) δ 160.7, 156.3, 153.4, 150.2, 139.6, 117.9, 114.9, 100.1, 71.6, 27.7; MS *m*/*z* (%) (EI): 244 (26) $[M]^+$, 230 (13), 229 (97), 202 (22), 201 (100), 187 (21), 186 (49), 159 (44), 136 (23), 135 (29), 119 (13), 108 (18), 92 (17), 81 (31), 67 (40), 66 (41), 65 (18), 59 (38), 54 (16), 53 (17), 52 (17); UV λ_{max} (log ε) (ethanol): 208 (4.41), 258 (4.19) nm. Anal. Calcd for $C_{11}H_{12}N_6O$: C, 54.09; H, 4.95; N, 34.41. Found: C, 53.79; H, 5.05; N, 34.26.

*4.3.2. (Z)-3-(6-Amino-9H-purin-9-yl)-4-hydroxy-4-methyl-2-hexenenitrile **3b**.* Method A: 245 mg, yield 95%; method C: 115 mg, yield 56%, light beige crystals; mp 208–214 °C; IR (KBr) 3430, 3321, 3264, 3174 (NH_2, OH), 3066 (C=CH), 2225 (CN), 1661, 1638, 1600 (NH_2, C=C), 1571, 1506, 1480 (C=N) cm^{-1}; ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 8.17 (s, 1H), 8.16 (s, 1H), 7.40 (s, 2H), 6.49 (s, 1H), 5.62 (s, 1H), 1.56–1.49 (m, 1H), 1.47–1.40 (m, 1H), 1.30 (s, 3H), 0.86 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (100.61 MHz, DMSO-d_6) δ 159.9, 156.3, 153.3, 150.1, 139.5, 117.9, 115.0, 100.7, 74.1, 32.1, 25.1, 7.7; ^{15}N NMR (40.56 MHz, DMSO-d_6) δ −298.1 ($^1J_{NH}$=90.3 Hz), −216.4, −154.7, −142.9, −137.7, −113.1; MS *m*/*z* (%) (EI): 258 (2) $[M]^+$, 229 (18), 215 (17), 136 (11), 135 (23), 108 (14), 67 (37), 66 (36), 65 (15), 55 (23), 54 (21), 53 (35), 52 (18), 51 (10), 45 (14), 44 (12), 43 (100), 42 (14), 41 (16), 40 (66); UV λ_{max} (log ε) (ethanol): 208 (4.44), 258 (4.20) nm. Anal. Calcd for $C_{12}H_{14}N_6O$: C, 55.80; H, 5.46; N, 32.54. Found: C, 55.94; H, 5.76; N, 32.58.

*4.3.3. (Z)-3-(6-Amino-9H-purin-9-yl)-3-(1-hydroxycyclopentyl)-2-propenenitrile **3c**.* Method A: 262 mg, yield 97%; method C: 259 mg, yield 96%; light beige crystals, mp 232–235 °C; IR (KBr) 3432, 3321, 3257, 3154 (NH_2, OH), 3061, 2985 (C=CH), 2225 (CN), 1662, 1640, 1600 (NH_2, C=C), 1573, 1511, 1482 (C=N) cm^{-1}; ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 8.18 (s, 1H), 8.17 (s, 1H), 7.40 (s, 2H), 6.53 (s, 1H), 5.77 (s, 1H), 1.29 (s, 8H); ^{13}C NMR (100.61 MHz, DMSO-d_6) δ 160.7, 156.2, 153.3, 150.1, 139.6, 117.9, 114.9, 100.0, 71.6, 27.7; MS *m*/*z* (%) (EI): 270 (5) $[M]^+$, 229 (11), 201 (12), 135 (10), 67 (26), 66 (30), 65 (12), 59 (20), 54 (12), 53 (20), 52 (11), 43 (100), 42 (12), 41 (19), 40 (25); UV λ_{max} (log ε) (ethanol): 209 (4.36), 258 (4.12) nm. Anal. Calcd for $C_{13}H_{14}N_6O$: C, 57.77; H, 5.22; N, 31.09. Found: C, 57.61; H, 5.42; N, 31.41.

*4.3.4. (Z)-3-(6-Amino-9H-purin-9-yl)-3-(1-hydroxycyclohexyl)-2-propenenitrile **3d**.* Method A: 273 mg, yield 96%; method C: 76 mg, yield 72%; beige crystals, mp 236–240 °C; IR (KBr) 3434, 3321, 3259, 3157 (NH_2, OH), 3061 (C=CH), 2226 (CN), 1662, 1643, 1600 (NH_2, C=C), 1574, 1510, 1480 (C=N) cm^{-1}; ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 8.20 (s, 1H), 8.19 (s, 1H), 7.46 (s, 2H), 6.54 (s, 1H), 5.60 (s, 1H), 1.59–1.16 (m, 10H); ^{13}C NMR (100.61 MHz, DMSO-d_6) δ 161.1, 156.6, 153.6, 150.5, 139.9, 118.2, 115.4, 100.7, 72.9, 34.5, 24.9, 21.2; MS *m*/*z* (%) (EI): 284 (34) $[M]^+$, 267 (42), 266 (27), 265 (20), 256 (22), 241 (14), 229 (14), 228 (19), 227 (29), 216 (15), 214 (29), 213 (39), 200 (23), 188 (28), 187 (53), 186 (38), 175 (15), 160 (16), 159 (34), 134 (94), 135 (100), 132 (22), 119 (19), 108 (40), 105 (18), 93 (15), 92 (26), 81 (31), 79 (19), 67 (58), 66 (49), 65 (22), 57 (18), 55 (56), 54 (24), 53 (31), 52 (19), 45 (19); UV λ_{max} (log ε) (ethanol): 209 (4.57), 261 (4.37) nm. Anal. Calcd for $C_{14}H_{16}N_6O$: C, 59.14; H, 5.67; N, 29.56. Found: C, 59.49; H, 5.46; N, 29.37.

4.4. Reaction of 8-azaadenine 6 with α,β-acetylenic γ-hydroxy nitriles 2a–d

4.4.1. General method. To mixture of 8-azaadenine **6** (136 mg, 1.0 mmol) and Et_3N (30 mg, 30 mol %), the appropriate acetylenes **2a–d** (2.0 mmol) were added at rt and stirred for 12–38 h. The reaction mixture was sequentially treated acetone and diethyl ether, the residue was dried in vacuo to give compounds **8a–d**.

*4.4.1.1. (Z)-3-(7-Amino-2H-[1,2,3]triazolo[4,5-d]pyrimidin-2-yl)-4-hydroxy-4-methyl-2-pentenenitrile **8a**.* Yield 220 mg, 90%, white powder, mp 222–224 °C (decomp.); IR (KBr) 3434, 3378, 3346 (NH_2, OH), 3051 (C=CH), 2228 (CN), 1671, 1641, 1603 (NH_2, C=C), 1577, 1482 (C=N) cm^{-1}; ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.40 (s, 1H), 8.38 (s, 1H), 6.67 (s, 1H), 5.99 (s, 1H), 1.43 (s, 6H); ^{13}C NMR (100.61 MHz, DMSO-d_6) δ 165.8, 158.9, 158.3, 157.6, 127.7, 115.2, 98.6, 72.7, 28.8; ^{15}N NMR (40.56 MHz, DMSO-d_6) δ −150.1, −147.0, −122.3, −111.5, −64.3; MS *m*/*z* (%) (EI): 245 (6) $[M]^+$, 230 (10), 217 (14), 159 (10), 132 (18), 110 (100), 105 (11), 82 (22), 81 (11), 67 (36), 66 (38), 65 (14), 61 (10), 59 (47), 55 (19), 54 (21), 53 (26), 52 (16), 45 (10), 44 (23), 43 (93), 42 (20), 41 (38), 40 (40); UV λ_{max} (log ε) (ethanol): 207 (4.40), 240 (4.14), 279 (4.00), 309 (4.02) nm. Anal. Calcd for $C_{10}H_{11}N_7O$: C, 48.98; H, 4.52; N, 39.98. Found: C, 48.65; H, 4.79; N, 39.72.

*4.4.1.2. (Z)-3-(7-Amino-2H-[1,2,3]triazolo[4,5-d]pyrimidin-2-yl)-4-hydroxy-4-methyl-2-hexenenitrile **8b**.* Yield 186 mg, 72%, white powder, mp 210–212 °C (decomp.); IR (KBr) 3387, 3338, 3126 (NH_2, OH), 3064 (C=CH), 2225 (CN), 1673, 1638, 1604 (NH_2, C=C), 1572 (C=N) cm^{-1}; ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.39 (s, 1H), 8.38 (s, 1H), 6.62 (s, 1H), 5.86 (s, 1H), 1.80–1.75 (m, 1H), 1.68–1.61 (m, 1H), 1.38 (s, 3H), 0.86 (t, *J*=7.2 Hz, 3H); ^{13}C NMR

(100.61 MHz, DMSO-d_6) δ 164.1, 158.5, 157.8, 157.1, 127.3, 114.8, 99.2, 74.8, 32.5, 26.7, 7.9; ^{15}N NMR (40.56 MHz, DMSO-d_6) δ −150.2, −147.0, −122.4, −111.7, −64.6; MS m/z (%) (EI): 259 (3) $[M]^+$, 230 (19), 67 (12), 66 (10), 55 (20), 54 (19), 53 (44), 52 (11), 43 (100), 42 (13), 41 (11), 40 (19); UV λ_{max} (log ε) (ethanol): 207 (4.26), 240 (4.05), 279 (3.88), 309 (3.91) nm. Anal. Calcd for $C_{11}H_{13}N_7O$: C, 50.96; H, 5.05; N, 37.82. Found: C, 51.29; H, 4.95; N, 37.46.

4.4.1.3. (Z)-3-(7-Amino-2H-[1,2,3]triazolo[4,5-d]pyrimidin-2-yl)-3-(1-hydroxycyclopentyl)-2-propenenitrile ***8c***. Yield 119 mg, 44%, white powder, mp 214–217 °C (decomp.); IR (KBr) 3361, 3181, 3161 (NH_2, OH), 3051 (C═CH), 2232 (CN), 1670, 1640, 1593 (NH_2, C═C), 1566 (C═N) cm^{-1}; ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.40 (s, 1H), 8.38 (s, 1H), 6.70 (s, 1H), 5.73 (s, 1H), 1.95–1.59 (m, 8H); ^{13}C NMR (100.61 MHz, DMSO-d_6) δ 164.2, 158.8, 158.2, 157.5, 127.7, 115.2, 99.1, 82.5, 24.2; ^{15}N NMR (40.56 MHz, DMSO-d_6) δ −149.8, −146.8, −122.2, −111.7, −64.3; MS m/z (%) (EI): 271 (5) $[M]^+$, 136 (34), 81 (41), 67 (32), 66 (28), 65 (23), 56 (10), 55 (39), 54 (50), 53 (100), 52 (20), 51 (15), 43 (98), 42 (63), 41 (94), 40 (55); UV λ_{max} (log ε) (ethanol): 209 (4.34), 240 (4.08), 309 (3.93) nm. Anal. Calcd for $C_{12}H_{13}N_7O$: C, 53.13; H, 4.83; N, 36.14. Found: C, 53.09; H, 4.96; N, 36.28.

4.4.1.4. (Z)-3-(7-Amino-2H-[1,2,3]triazolo[4,5-d]pyrimidin-2-yl)-3-(1-hydroxycyclohexyl)-2-propenenitrile ***8d***. Yield 148 mg, 52%, white powder, mp 216–220 °C (decomp.); IR (KBr) 3437, 3335, 3190 (NH_2, OH), 3066 (C═CH), 2227 (CN), 1671, 1643, 1605 (NH_2, C═C), 1573 (C═N) cm^{-1}; ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.38 (s, 1H), 8.36 (s, 1H), 6.72 (s, 1H), 5.70 (s, 1H), 1.71–1.47 (m, 10H); ^{13}C NMR (100.61 MHz, DMSO-d_6) δ 163.3, 158.9, 158.7, 158.6, 127.8, 115.4, 100.6, 74.3, 34.8, 25.2, 21.4; ^{15}N NMR (40.56 MHz, DMSO-d_6) δ −149.8, −146.8, −122.2, −111.7, −64.3; MS m/z (%) (EI): 285 (3) $[M]^+$, 136 (11), 110 (10), 81 (26), 67 (22), 66 (33), 65 (12), 56 (11), 55 (44), 54 (28), 53 (62), 52 (10), 51 (10), 44 (16), 43 (51), 42 (28), 41 (79), 40 (100); UV λ_{max} (log ε) (ethanol): 209 (4.23), 240 (3.90), 300 (3.79) nm. Anal. Calcd for $C_{13}H_{15}N_7O$: C, 54.73; H, 5.30; N, 34.37. Found: C, 54.87; H, 5.44; N, 34.43.

4.4.1.5. Reaction of the 8-azaadenine ***6*** *with acetylene* ***2a*** *in the presence of K_2CO_3 in DMF.* To a suspension of 8-azaadenine **6** (137 mg, 1.0 mmol), K_2CO_3 (11 mg, 8 mol %) in DMF (1.5 mL), the acetylene **2a** (109 mg, 1.0 mmol) in DMF (1.5 mL) was added at rt. The reaction mixture was stirred for 1 h. The resulting mixture was passed through neutral Al_2O_3 (0.5 cm, eluent: 3 mL of DMF) and then solvent was evaporated in vacuo. The residue was treated with diethyl ether and dried in vacuo to give 210 mg of crude product consisting from *N*-8—(*Z*)-3-(7-amino-2*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-2-yl)-4-hydroxy-4-methyl-2-pentenenitrile **8a** (41.5%), *N*-9—(*Z*)-3-(7-amino-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)-4-hydroxy-4-methyl-2-pentenenitrile **9** (35.5%) and N-7—(*Z*)-3-(7-amino-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-1-yl)-4-hydroxy-4-methyl-2-pentenenitrile **7** (4%) (^{1}H NMR data), total yield 81%.

For **7**: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 8.68 (br s, 1H), 8.44 (br s, 1H), 8.38 (s, 1H), 6.65 (s, 1H), 5.93 (s, 1H), 1.33 (s, 6H).

For **9**: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 8.68 (br s, 1H), 8.38 (s, 1H), 8.34 (br s, 1H), 6.70 (s, 1H), 5.93 (s, 1H), 1.33 (s, 6H); ^{13}C NMR (100.61 MHz, DMSO-d_6) δ 161.8, 158.1, 156.6, 150.1, 123.1, 114.6, 101.1, 72.4, 28.0; ^{15}N NMR (40.56 MHz, DMSO-d_6) δ −163.1 ($^2J_{NH}$=15.9 Hz), −149.8, −144.9 ($^2J_{NH}$=16.4 Hz), −122.0, −112.1.

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