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Modification of guanosine with cyanopropargylic alcohols

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ABSTRACT

Guanosine has been modified with tertiary cyanopropargylic alcohols under mild conditions (1:1.1–2 molar ratio, K_2CO_3, DMF, 20–25 °C, 19–50 h) to simultaneously give two modifications. The first product (1:1 adduct) is formed by the stereoselective addition of the amide function of the purine ring to the triple bond (38–43% yields), and the second product is the 1:2 adduct, with a second molecule of cyanopropargylic alcohol having reacted with the two vicinal hydroxy groups of the ribose moiety to give a functionalized 1,3-dioxolane ring (29–50% yields).

Guanosine is an important nucleoside and metabolite[1] possessing anti-oxidant and radioprotective properties, and protects DNA in vitro from damage by reactive oxygen species.[2] It is incorporated in nucleic acids and biologically active guanyl nucleotides.[3] Guanosine derivatives are effective against viruses such as vesicular stomatitis, vaccinia, and herpes viridae.[4] Compounds with guanosine modifications are also specific irreversible inhibitors of RNA-polymerase[5] and suppress the replication of HIV reverse transcriptase.[6] The guanosine derivative, cadeguomycin, inhibits tumor growth and metastasis in association with modification of the immune system.[7] Many known drugs (antiviral medicines: aciclovir, ganciclovir, penciclovir, and valaciclovir) are examples of modified guanosines.[8] However, these guanosine derivatives are modified at the nitrogen atom at position 9, probably due to the lower reactivity of other positions, for example, the amide nitrogen (N-1). Indeed, the purine moiety has been modified with halo- and unsaturated compounds (C=O, C=C, C≡N, and N=C–O) to deliver derivatives in low yields and with incomplete conversion of the guanosine.[9] The reaction of guanosine with chloroacetaldehyde gave N^2-ethenoguanosine (3-[3,4-dihydroxy-5-(hydroxymethyl) tetrahydro-2-furanyl]-3,5-dihydro-9*H*-imidazo[1,2-*a*]purin-9-one) in only 7.5% yield.[9b] The treatment of guanosine with methyl-*N*-cyanomethanimidate led to an annelated product involving N-1 (in 39% yield).[9c,d] When dioxyguanosine was reacted with methyl vinyl ketone, annelation with piperidine ring took place (yield 5–10%).[9e] 8-Bromoguanosine was cross-coupled with phenylacetylene in the presence of $Pd(PPh_3)_2Cl_2$, the yield of the target 8-(phenylethynyl)guanosine being 20%. The same reaction, but in the presence of Amberlite IRA-67 (other conditions being similar), gave the cross-coupled product in 83% yield.[9h] Furthermore, it might be expected that elaboration of easier modifications of other guanosine positions would open a route to additional opportunities for guanosine drug design.

Some other modifications of guanosine relate to its ribose moiety. Refluxing guanosine in acetone for five hours in the presence of $ZnCl_2$ gave a 1,3-dioxolane derivative involving the two vicinal groups at positions 2′ and 3′.[10a,b] In addition, the synthesis of a cyclic diguanosine monophosphate, a bacterial signaling molecule, with thiourea, urea, carbodiimide, and guanidinium linkages between the ribose moieties was recently realized.[10d]

The above examples show that guanosine-based medicines originating from guanosine modification remain challenging targets in current drug design. Therefore, the search for novel and straightforward approaches to guanosine modification represents an important task in modern organic synthesis. An uncommon route to new functionalized guanosine derivatives is the modification of guanosine with reactive acetylenic compounds.

Indeed, data on the successful modification of guanosine with acetylenes are lacking in the literature. It has been mentioned that guanosine, in contrast to adenosine, does not react with alkyl 4-chloro-2-butynoate esters or ethyl propiolate.[11] Recently, we succeeded in modifying adenosine and cytidine with cyanopropargylic alcohols, the former reacting with the two vicinal hydroxyls,[12a] while the latter reacted with all three hydroxyls of the ribose moiety.[12b] Thus, readily accessible cyanopropargylic alcohols[13] prove to be novel and prospective modifying agents for the nucleoside family, allowing simultaneous introduction of hydroxy and cyano

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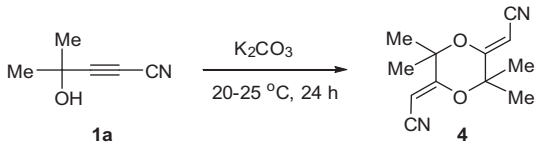
functions as well as ethylenic and acetal moieties. To extend this chemistry, we decided to investigate whether cyanopropargylic alcohols were also applicable for the modification of guanosine, which has so far remained poorly reactive toward common reactive acetylenes.

Here, we report the first examples of guanosine modification with acetylenic compounds, specifically cyanopropargylic alcohols. After optimization, we found that guanosine reacts stereoselectively with cyanopropargylic alcohols **1a–d** under mild conditions (30–50 mol % K_2CO_3, DMF, 20–25 °C, 19–50 h) to afford simultaneously two modifications (Table 1). The first is 1:1 adducts **2a–d** in 38–43% yields with *Z*-configuration on the amide moiety of the purine, and with the ribose moiety remaining intact. The second is the 1:2 adducts **3a–d** with another molecule of the acetylene **1a–d** attached to the ribose moiety via its two vicinal hydroxy groups at positions 2′ and 3′ to form a 1,3-dioxolane, in 29–50% yield.[14]

Completion of the reactions was monitored by TLC up to the disappearance of the starting acetylene spot. Owing to different reactivities of the reactants, the reaction times shown in Table 1 vary.

The molar ratio of the reactants influences the yields of the modifications and conversion of guanosine (Table 1). At a guanosine:**1a** molar ratio of 1:1.1 (50 mol % K_2CO_3), the yields of products **2a** and **3a** were 43% and 32%, respectively. In the presence of 30 mol % of K_2CO_3 the yields of products **2a** and **3a** were 22% and 13%, respectively. The reaction with a two-fold molar excess of acetylene **1a** gave 40% and 50% yields of **2a** and **3a**, respectively, while for acetylenes **1c**,**d**, at the same molar ratios, the yields of **2c**,**d** and **3c**,**d** were 44% and 38% and 35% and 29%, respectively.



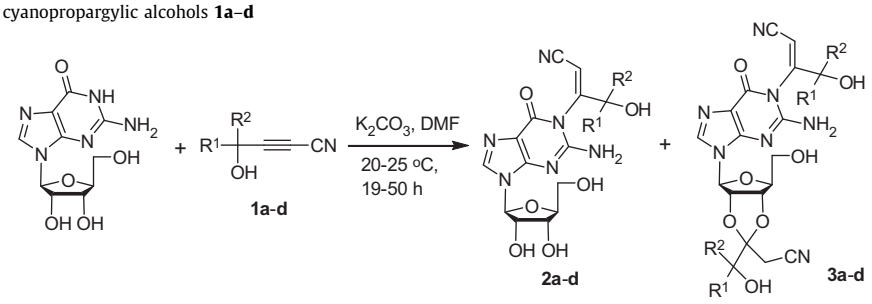
Scheme 1. Dimerization of 4-hydroxy-4-methyl-2-pentynenitrile (**2a**).

An attempt to accomplish this reaction under solvent-free conditions using a 10-fold excess of solid K_2CO_3[15] (guanosine/**1**/K_2CO_3 = 1:1:10 by weight, 20–25 °C, 24 h) led to cyclic dimerization of the starting cyanopropargylic alcohol **1a** to form 2,5-di(cyanomethylidene)-1,4-dioxane **4** (Scheme 1, yield 28%). Amazingly, no traces of the expected adducts were discernible in the reaction mixture in this case.

Trialkylamines, for example, Et_3N, showed no catalytic activity in this reaction. In the case of acetylene **1a**, with 50 mol % of Et_3N (no solvent, 20–25 °C, 24 h), 1,4-dioxane **4** was isolated in 45% yield. Under neat conditions (reaction temperature and time being the same), no reactions occurred.

Under the best conditions found, the reaction time depends on the starting acetylenes **1a–d**. In the case of acetylenes **1a**,**b**, the reaction required up to 24 h, whereas the complete consumption of acetylenes **1c**,**d** required 44 and 50 h. This is obviously a consequence of the steric screening of the reaction centers by the bulky cycloalkyl substituents. It is noteworthy that in no case was the step-wise addition of the hydroxy group to the triple bond observed (TLC). It follows that as soon as the first hydroxyl group is added to the triple bond, the neighboring vicinal hydroxyl closes

Table 1
Modification of guanosine with cyanopropargylic alcohols **1a–d**



Acetylene	R^1	R^2	Ratio of guanosine:**1** (mol)	Time (h)	Conversion of guanosine (%)	Product	Yield (%)
1a	Me	Me	1:1.1	20	—	**2a**[a]	22[b]
						3a[a]	13[b]
1a	Me	Me	1:1.1	19	78	**2a**	43[c]
						3a	32[c]
1a	Me	Me	1:2	24	82	**2a**	40[c]
						3a[d]	50[c]
1b	Me	Et	1:1.1	20	—	**2b**	19[b]
						3b	8[b]
1b	Me	Et	1:2	24	78	**2b**	36[c]
						3b	45[c]
1c	$(CH_2)_4$		1:1.1	30	—	**2c**	12[b]
						3c	6[b]
1c	$(CH_2)_4$		1:2	44	72	**2c**	44[c]
						3c	35[c]
1d	$(CH_2)_5$		1:1.1	30	—	**2d**	10[b]
						3d	7[b]
1d	$(CH_2)_5$		1:2	50	75	**2d**	38[c]
						3d[d]	29[c]

[a] In the presence of K_2CO_3 (30 mol %).
[b] Yield based on ^1H NMR spectroscopy.
[c] Isolated yield after preparative column chromatography (based on consumed guanosine).
[d] Ratio of diastereomers = 3:1.