Synthesis of Certain New 1,2,3-Triazole Acyclonucleosides *via* 1,3-Dipolar Cycloaddition

Smaail Radi[*] and Hassan B. Lazrek[†]

Laboratoire de Chimie Organique Physique, Faculté des Sciences-oujda, Maroc
[†]Laboratoire de Chimie Bio-organique, Faculté des Sciences-Semlalia, Marrakech/Maroc
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A variety of 1,2,3-triazole derivatives bearing acyclic sugar moieties of DHPG and iso-NDG were synthesised by Diels-Alder reaction. None of the new compounds display any interesting biological activity.

Keywords : Triazole, Cycloaddition, Azide, Acetylenic, Biological.

Introduction

The discovery of the two structural isomers acyclo-guanosines[1-6]: 9-(1,3-dihydroxy-2-propoxymethyl) guanine (DHPG, **1**) and 9-(2,3-dihydroxy-1-propoxymethyl) guanine (iso-NDG, **2**) (Figure 1) as the effective and highly selective antiviral drugs for the treatment of herpes simplex virus (HSV) infections has stimulated an extensive search for acyclic nucleosides that are more potent antiviral agents. So far, the structure-activity studies have shown that the side chain of acyclic nucleosides plays a main role in the antiviral activity (phosphorylation). Accordingly, many nucleoside chemists have directed their efforts toward the synthesis of analogues of ACV, DHPG (**1**), iso-NDG (**2**) and other acyclonucleosides with various side chains and aglycons. On the other hand, azole nucleosides are a large class of anti-metabolites. Important drugs of this class are brednin, pyrazofurin and ribavirin and its analogs,[7] which are endowed with immuno-suppressive, antitumor and antiviral activity, respectively.

The present investigation presents a convenient pathway for the preparation of a series of DHPG and iso-NDG analogues in which derivatives of 1,2,3-triazole replace guanine moiety. To lead to the new azole acyclonucleosides, the reaction was carried out *via* a 1,3-dipolar cycloaddition[8,9] between the acyclic sugar azides (1-functionalized acyclic sugar) beforehand prepared which react as diene with acetylene's dienophile. These compounds were then screened by *in vitro* studies for antiviral activities.

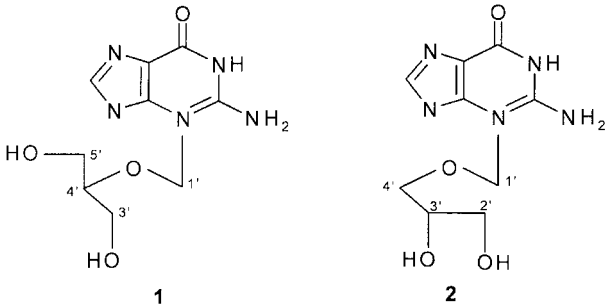


Figure 1. Structures of DHPG (**1**) and iso-NDG (**2**).

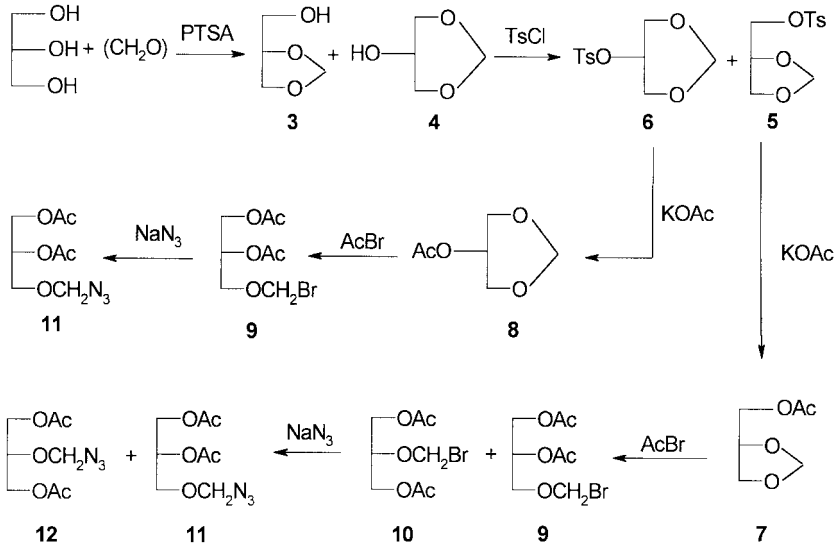
[*]Corresponding Author. Radi@sciences.univ-oujda.ac.ma

Results and Discussion

Preparation of acyclic sugar azides: Our strategy was to develop first a simple and convenient method for obtaining the acyclic sugar azides. The results of our investigation are given below (Scheme 1): The reaction of D-glycerol with paraformaldehyde catalysed by paratoluene sulfonic acid has been already reported[10] to give a mixture of glycerol formal **3** and **4**. The hydroxyl groups was actived with tosyl chloride to afford a mixture of isomers **5** and **6** which were separated in diethyl ether to give **5**/**6** in ratio 3/1. Substitution of tosyl group of each compounds **5** and **6** with KOAc in dry DMSO leads after extraction and distillation to acetyl compounds **7** (95%) and **8** (95%) respectively. In the ^{1}H NMR spectra of each **7** and **8** appeared a signal of acetyl groups and disappeared that of tosyl groups. Acylation of **7** at room temperature with acetyl bromide leads to the mixture of **9** and **10** in ratio 1/3 as shown by ^{1}H NMR. And the minor synthon **9** was equally obtained by acylation of **8** in 97% yield. Azides derivatives **11** as pure product and the mixture of **11**/**12** in ratio 1/3 were obtained from the substitution of the bromide group of **9** and **10** respectively with the azide group as shown in scheme 1, the IR spectra show a signal of N_3 group at 2092 cm^{-1}. Structures of all compounds were determined on the basis of the corresponding analytical and spectroscopic data (Table 1).

1,3-Dipolar cycloaddition of azides with acetylenic groups: A mixture of (**11** + **12**) and dimethyl acetylenedicarboxylate **15a** was refluxed in toluene for 72 hours (Scheme 3), provide the corresponding 1,2,3-triazole derivatives (**13** + **14**) in ratio 1/3 which were separated on silica gel column chromatography. The minor product **13** was equally obtained from the pure synthon **11** in the same procedure. (Scheme 2).

Also, other cycloaddition reaction could be readily carried out with methyl propiolate **15b** and diethyl ethynylphosphonate **15c**.[11] Reaction of **11** with **15b** or **15c** in refluxing toluene yielded one isolated major product **16** (65%) and **17** (73%) respectively (Scheme 2). A mixture of (**11** + **12**) and

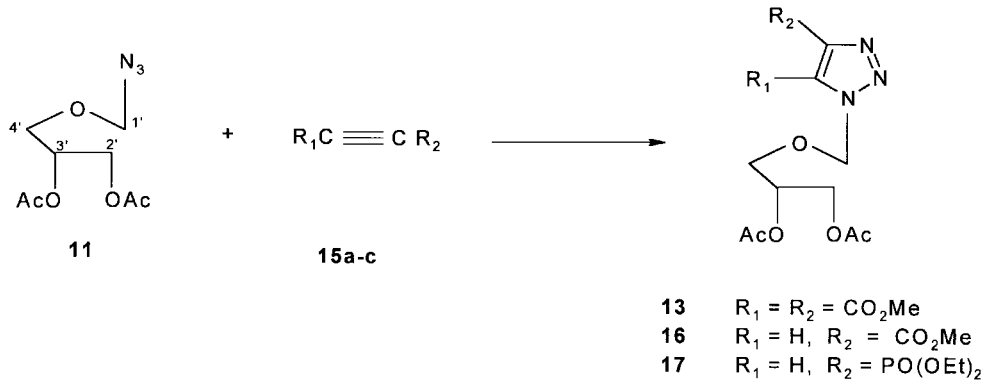


Scheme 1

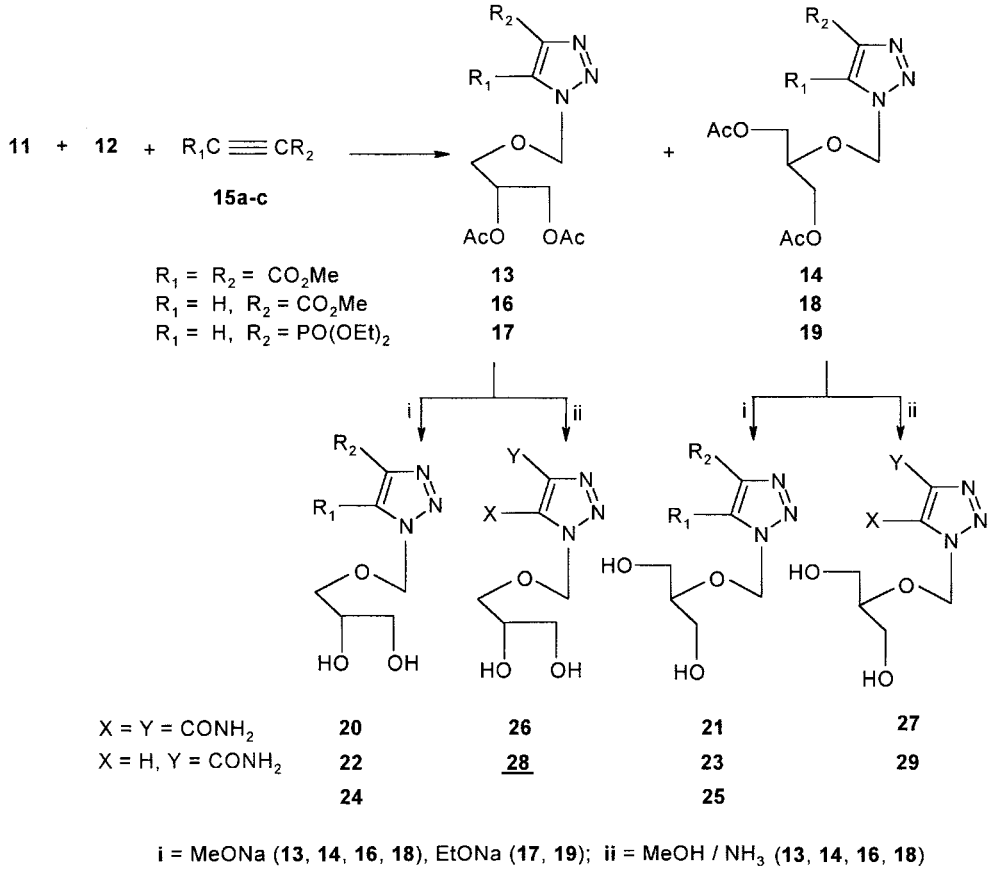
Table 1.

Compound No	Yield %	Bp (°C) (0.03 mmHg)	Mp (°C) (ether)	Calcd/Found (%) C	H	^{1}H-NMR* δ ($CDCl_3$)
3 / **4**	90 (3/2)	70-75		46.12	7.75	4.76 (s, 2), 4.90 (AB, 2), 3.50-4.10 (m, 10), 4.50 (bs, 2).
				46.20	7.79	
5	60		35-36	51.75	5.34	2.40 (s, 3), 3.80 (m, 4), 4.20 (m, 1), 4.80 (ab, 2), 7.80 (m, 4).
				51.04	5.21	
6	40		90-91	51.75	5.34	2.40 (s, 3), 3.85 (m, 4), 4.40 (m, 1), 4.70 (s, 2), 7.50 (m, 4).
				51.95	5.36	
7	95	61		49.30	6.83	2.02 (s, 3), 3.56-4.20 (m, 5), 4.76 and 4.90 (ab, 2).
				49.25	6.80	
8	95	62		49.30	6.83	2.06 (s, 3), 3.80 (m, 5), 4.73 (s, 2).
				49.45	6.90	
9	97	101-105		35.68	4.83	2.06 (s, 6), 3.50-4.30 (m, 4), 5.1 (m, 1), 5.70 (m, 2).
				35.42	4.79	
9 / **10**	95 (1/3)	101-105		35.68	4.83	2.06 (s, 12), 3.50-4.30 (m, 8), 5.17 (m, 2), 5.70 (m, 2), 5.80 (m, 2)
				35.73	4.91	
11	95	oil		41.55	5.62	2.00 (s, 3), 2.06 (s, 3), 4.00 (m, 4), 4.68 (s, 2), 5.10 (m, 1).
				41.38	5.50	
11 / **12**	95 (1/3)	oil		41.55	5.62	2.05 (s, 12), 3.43-4.30 (m, 8), 4.68 (s,2), 4.70 (s, 2), 5.13 (m, 2).
				41.67	5.71	

*The proton signals of the hydroxy group were detected by treatment of deuterium oxide. Abbreviations used: s: singulet, bs: broad singulet, ab: AB system, d: doublet, t: triplet, m: multiplet



Scheme 2



Scheme 3

each **15b** or **15c** under the same condition lead to the two isolated major products **16**/**18** or **17**/**19** respectively in ratio 1/3 (Scheme 3). The minor products **16** and **17** are identic with the products which were obtained in Scheme 2.

It is known from the literature that addition of azides to unsymmetrical acetylenes, is determined by steric and electronic factors. In general, such addition tends to give mainly the isomers with electron withdrawing groups at the 4-position and electron releasing groups at the 5-position.[12-14] On the other hand, the sterically less hindred isomers tend to be the major isomer.[15,16] A differentiation between DHPG and iso-NDG isomers analogues was determined on the basis of the chemical shifts of the sugar moiety. The isomers **13**, **16** and **17** analogues of iso-NDG show two assignments of acetyl groups (1.98 ppm and 2.03 ppm) and one multiple assignment of C-2', C-3' and C-4' protons. And the isomers **14**, **18** and **19** analogues of DHPG show one acetyl assignment (2.10 ppm) and one doublet assignment of symmetrical C-3' and C-5' protons (Table 2).

The acetyl groups in the sugar moiety of the newly compounds **13-19** was removed in each sodium methylate (for **13**, **14**, **16**, **18**)/ethylate (for **17**, **19**) and ammonia in methanol (for **13**, **14**, **16**, **18**) to give respectively (**20**, **21**, **22**, **23**)/(**24**, **25**) and (**26**, **27**, **28**, **29**) after treatment with Dowex H^+ 50×8 and flash column chromatography (Scheme 3). Structures of the final newly acyclonucleosides were determined on the basis of the corresponding analytical and spectroscopic data (Table 2).

Biological Screening

The compounds described in this manuscript were tested against the virus Herpes simplex (HSV-1, HSV-2), vesicular stomatitis (VSV), vaccina (VV), cytomegalovirus (CMV), parainfluenza 3 (PIV) and were found to be inactive. Activities against HIV-1 were carried out using CEM-SS cells at 10^{-4} M.

Experimental Section

All melting points were determined with a Büchi apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded with a 250 MHz Bruker AC-250 spectrometer. Chemical shifts are reported in parts per million (d) using internal TMS standard. Thin-layer chromatography was performed on silica gel 60F-254 plates. Column chromatography was performed on silica gel (0.0063-0.2 mm, Merck). The mass spectrum was optained on a Jeol JMX-DX 300. Infrared spectral data were obtained on a Hitachi 270-50 spectres photometer. The compounds were analysed for C, H and N. The results were within 0.4% of the calculated theoretic values.

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Table 2.

Compound No	Yield %	m/z (M^+)	Mp (°C)	Calcd/Found (%)			Solvent	^{1}H-NMR
				C	H	N		
13	73 (from **11**)	373	oil	45.04	5.09	11.26	$CDCl_3$	1.98 (s, 3), 2.03 (s, 3), 3.60-4.10 (m, 5),
	20 (from **11**+**12**)			45.00	4.95	11.15		3.95 (s, 3), 4.00 (s, 3), 5.90 (s, 2)
14	57	373	–	45.04	5.09	11.26	$CDCl_3$	2.10 (s, 6), 3.66 (s, 3), 3.90 (s, 3), 4.20 (d, 4),
				45.01	5.02	11.20		5.23 (m, 1), 5.90 (s, 2).
16	67 (from **11**)	315	–	45.71	5.39	13.33	$CDCl_3$	1.99 (s, 3), 2.03 (s, 3), 3.70-4.10 (m, 5),
	18 (from **11**+**12**)			45.65	5.25	13.27		3.93 (s, 3), 5.85 (s, 2), 8.50 (s, 1).
18	52	315	–	45.71	5.39	13.33	$CDCl_3$	2.10 (s, 6), 3.93 (s, 3), 3.55 (d, 4), 4.55 (m, 1),
				45.69	5.28	13.25		6.03 (s, 2), 8.03 (s, 1).
17	74 (from **11**)	393	–	42.74	6.10	10.68	DMSO-d_6	1.25 (t, 6), 1.92 (s, 3), 1.98 (s, 3), 4.10 (m, 9),
	20 (from **11**+**12**)			42.65	6.05	10.50		5.82 and 5.90 (ab, 2), 8.85 (s, 1).
19	54	393	–	42.74	6.10	10.68	DMSO-d_6	1.25 (t, 6), 1.91 (s, 3), 1.97 (s, 3), 4.10 (m, 9),
				42.69	6.01	10.53		5.92 and 5.99 (ab, 2), 8.27 (s, 1).
20	98	289	–	41.52	5.19	14.53	DMSO-d_6	3.25-3.50 (m, 5), 3.88 (s, 3), 3.95 (s, 3), 4.55
				41.46	5.08	14.41		(t, 1), 4.85 (d, 2), 5.95 (s, 2).
21	98	289	–	41.52	5.19	14.53	DMSO-d_6	3.20-3.45 (m, 5), 3.88 (s, 3), 3.92 (s, 3), 4.55
				41.42	5.10	14.46		(t, 1), 4.75 (t, 1), 5.95 (s, 2).
22	98	231	–	41.56	5.66	18.17	DMSO-d_6	3.20-3.45 (m, 5), 3.30 (s, 3), 4.60 (t, 1), 4.85
				41.45	5.50	18.37		(d, 1), 5.80 (s, 2), 8.95 (s, 1).
23	98	231	–	41.56	5.66	18.17	DMSO-d_6	3.55 (d, 4), 3.85 (s, 3), 4.30 (m, 1), 4.65 (t, 1),
				41.48	5.60	18.30		5.95 (t, 1), 5.80 (s, 2), 8.35 (s, 1).
24	98	309	–	38.83	6.47	27.18	DMSO-d_6	1.25 (t, 6), 3.25-3.80 (m, 5), 4.10 (q, 4), 4.70
				38.71	6.50	27.08		(m, 2), 5.80 and 5.90 (ab, 2), 8.85 (d, 1, J = 7).
25	98	309	–	38.83	6.47	27.18	DMSO-d_6	1.25 (t, 6), 3.70 (m, 5), 4.05 (q, 4), 4.95 (m, 2),
				38.73	6.41	27.10		5.82 and 5.95 (ab, 2), 8.27 (d, 1, J = 7).
26	98	259	156 (EtOH)	37.07	5.05	27.07	DMSO-d_6	3.20-3.60 (m, 5), 4.50 (t, 1), 4.75 (d, 1), 6.15
				37.07	5.01	26.95		(s, 2), 8.15 (bs, 2), 8.55 (bs, 1), 10.15 (s, 1).
27	95	259	oil	37.07	5.05	27.07	DMSO-d_6	3.50 (d, 4), 3.90 (m, 1), 4.80 (m, 2), 6.15
				37.00	5.01	27.01		(s, 2), 8.10 (bs, 2), 8.50 (bs, 1), 10.20 (bs, 1).
28	98	216	143 (EtOH)	38.88	5.59	25.91	DMSO-d_6	3.20-3.60 (m, 5), 4.55 (t, 1), 4.80 (d, 1), 5.80
				38.59	5.31	26.06		(s, 2), 7.50 (bs, 1), 7.90 (bs, 1), 8.65 (s, 1).
29	97	216	97 (EtOH)	38.88	5.59	25.91	DMSO-d_6	3.20 (d, 4), 3.55 (m, 1), 4.45 (bs, 1), 4.75 (bs, 1),
				38.70	5.40	26.03		6.00 (s, 2), 7.90 (bs, 1), 8.24 (bs, 1), 8.25 (s, 1).

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