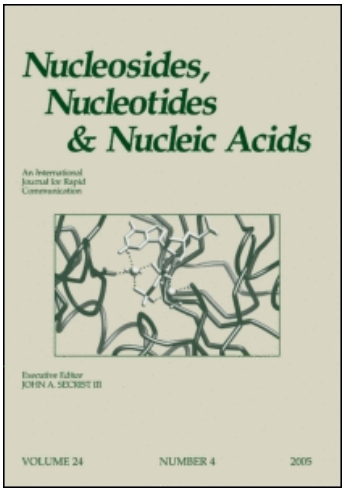

Nucleosides, Nucleotides and Nucleic Acids

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Alkyne-Azide Click Chemistry Mediated Carbanucleosides Synthesis

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ALKYNE-AZIDE CLICK CHEMISTRY MEDIATED CARBANUCLEOSIDES SYNTHESIS

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□ Hitherto *unknown 1,4-disubstituted-[1,2,3]-triazolo-4′,4′-dihydroxymethyl-3′-deoxy carbanucleosides were synthesized based on a "click approach." Various alkynes were introduced on a key azido intermediate by the "click" 1,3-dipolar Huisgen cycloaddition. Their antiviral activities and cellular toxicities were evaluated on vaccinia virus. None of the synthesized compounds exhibited a significant antiviral activity.*

Keywords Click chemistry; Huisgen cycloaddition; carbanucleosides; alkyne-azide

INTRODUCTION

The recent emergence of life threatening viral diseases such as AIDS, hepatitis, herpes, smallpox, and so on, has been a living force for the development of small nucleoside libraries.[1] Particularly, analogues of nucleosides structurally related to ribavirin have focused much interest as potent inhibitors of the inosine monophosphate dehydrogenase (IMPDH), which

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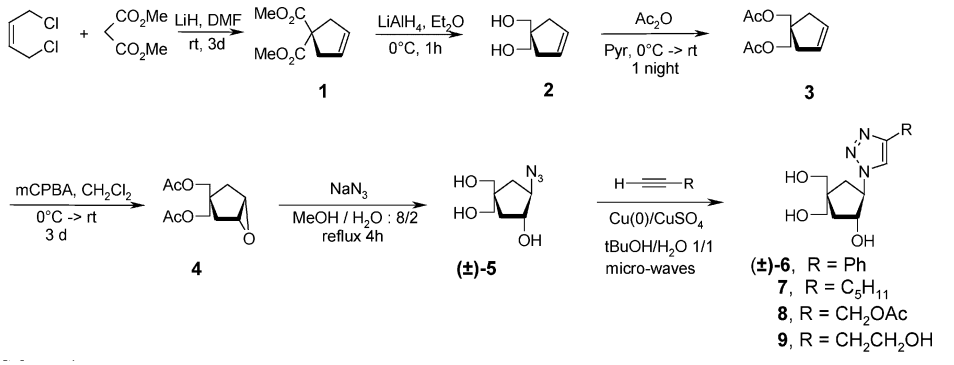

SCHEME 1

is a requirement for cell replication as this enzyme is involved in de novo guanine synthesis.[2] Thus, as part of our drug discovery group, we demonstrate herein the efficient microwave assisted synthesis of hitherto unknown 1,2,3-triazolo-carbocyclic nucleosides, an important pharmaceutical class, through a unique "click" approach. Indeed, the Cu(I)-catalyzed alkyne-azide 1,3-dipolar cycloaddition, Huisgen reaction,[3–5] recently has emerged as a powerful and selective reaction to form heteroatom links, and to leads to 1,4-disubstituted-1,2,3-triazolo analogues.[6] This transformation has been described as "click chemistry" as it affords products insensitive to oxygen and water, in high yields, and without any purification.

RESULTS AND DISCUSSION

The synthetic strategy of the present study is depicted in Scheme 1. The cyclopent-3-ene diester **1** was obtained from a malonic synthesis starting with the commercially available methyl malonate and the *cis*-1,4-dichloro-2-butene. After reduction of the diester **1**, the diol **2** was acetylated, and the resulting product **3** was reacted with 3-chloroperoxybenzoic acid to give the epoxide **4** with good yield. Finally, the azido-carbocycle **5** was obtained after the nucleophilic ring opening of the strained heterocycle **4** by sodium azide. This step involves also the deacetylation of the acetylated diols. Various 1,2,3-triazolo carbanucleosides **(6–9)** were then synthesized under the Huisgen conditions. Under a microwave assisted 1,3-dipolar cycloaddition, various alkynes were reacted with the azido-carbocycle **5** (Table 1). The mixture copper/copper sulfate Cu(0)/$CuSO_4$(II) in situ comproportionated was chosen as catalyst in a water and *tert*-butanol co-solvent. All the cycloadditions were realized with a rapid complete conversion of the azido-carbocycle into the desired carbanucleoside.

According to the carbanucleosides, the work-up was slightly different. The 1,4-disubstituted triazoles obtained from alkynes with a non-polar

TABLE 1 Microwave assisted Huisgen 1,3-dipolar cycloaddition

			Microwave 125°C		
Entry	Alkynes	Products	Time	Conversion (%)	Yield (%)
1	Phenylacetylene	**6**	2 min	100	98
2	Heptyne	**7**	1 h	100	98
3	Propargyl acetate	**8**	Immediate	100	95
4	3–Butyn-1-ol	**9**	2 min	100	95

substituent (phenylacetylene and heptyne (entries 1–2)) were isolated with very good yields after a simple extraction in ethyl acetate. The 1,4-disubstituted triazoles obtained from alkynes with a polar substituent (propargyl acetate and butynol (entries 3–4)) needed a filtration on silica gel column chromatography to eliminate the salts, since the products had too much affinity for the aqueous layer.

The regioselectivity of the ligation leading to 1,4-disubstituted-[1,2,3]-triazole moiety was confirmed by NMR using $^{1}H,^{13}C$ long range correlation spectra (HMBC) (Figure 1). The 50% inhibitory concentration (IC_{50}) of the synthesized compounds was evaluated in Vaccinia virius (VV) cells. The synthesized products did not show any cytotoxicity nor significant antiviral activity on VV.

In summary, the first synthesis of hitherto unknown 1,4-disubstituted-[1,2,3]-triazolo-4′,4′-dihydroxymethyl-3′-deoxycarbanucleosides have been

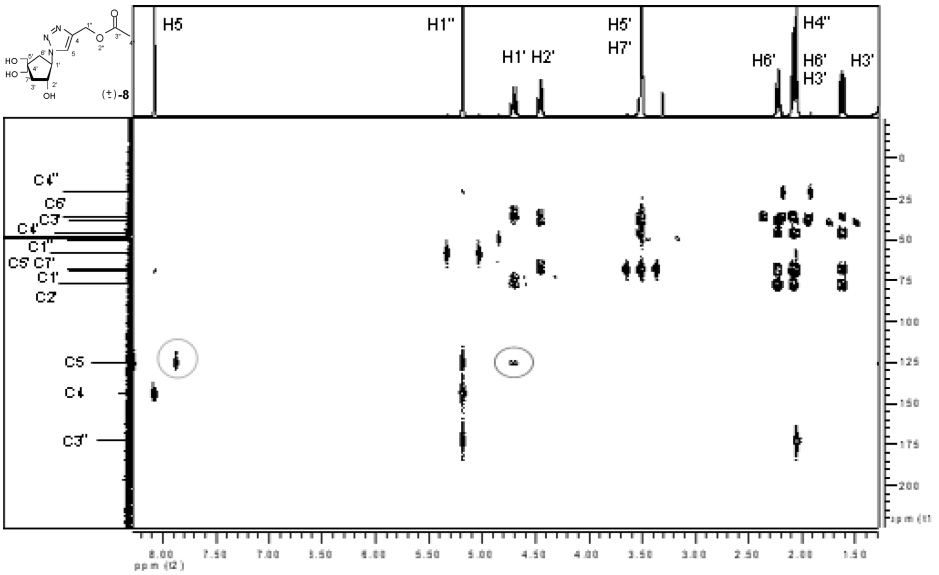

FIGURE 1 $^{1}H,^{13}C$ long range correlation NMR spectrum (HMBC) of (±) **(8)**.

accomplished using the 1,3-dipolar Huisgen cycloaddition under optimized click chemistry conditions.

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