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Click Approach to the Synthesis of 2,6-Bis(1,2,3-triazolyl)purine Deoxynucleosides

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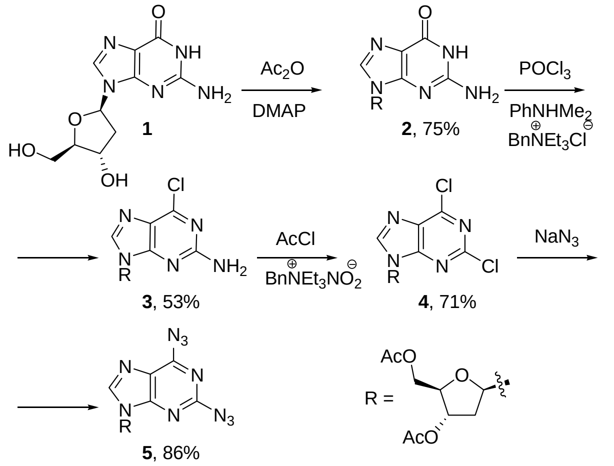
Azide-alkyne 1,3-dipolar cycloaddition reaction (*click* reaction) has been found to be useful in nucleoside, nucleotide and oligonucleotide chemistry. In recent years a number of 1,2,3-triazolylnucleoside derivatives have been synthesized and investigated, leading to discovery of substances with antiviral and anticancer activity, enzyme inhibitors, adenosine receptor agonists and antagonists [1]. Recently, our research group has reported the synthesis of ribofuranosyl and arabinopyranosyl nucleosides containing various 2,6-bistriazolyl purine moieties [2]. Reactions of the latter with amine nucleophiles were also investigated. The aim of this research is the synthesis of various 2,6-bistriazolyl deoxynucleoside derivatives using deoxyguanosine as starting material.

The key intermediate **5** was obtained in four steps from deoxyguanosine (Scheme 1). Hydroxyl groups in sugar residue were protected in DMAP-catalyzed reaction between deoxyguanosine **1** and acetic anhydride in pyridine at 20–30°C. Resulting **2** reacted with $POCl_3$ in dry acetonitrile at 85°C for 10 minutes in the presence of *N,N*-dimethylaniline and *N*-benzyl-*N,N,N*-triethylammonium chloride to give **3** [5]. In the following reaction with *N*-benzyl-*N,N,N*-triethylammonium nitrite and acetyl chloride in dry DCM dichloro derivative **4** was obtained [6]. Treatment with sodium azide in ethanol resulted in **5**. The reaction sequence **1**→**5** gave 24% overall yield.

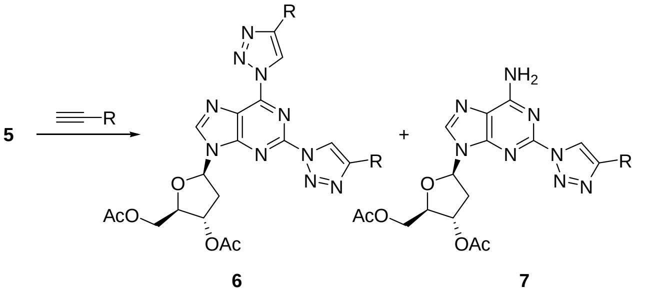


Scheme 1. Synthesis of 9-(di-*O*-acetyl-*β-D*-2-deoxyribofuranosyl)-2,6-diazidopurine (**5**)

Cycloaddition reactions (Scheme 2) between diazide **5** and different terminal alkynes were carried out in *tert*-butanol-water solution at room temperature using $CuSO_4{\cdot}5H_2O$, sodium ascorbate and acetic acid as a catalyst generating system. Typically, 5-fold excess of an alkyne and 30 mol% of acetic acid were used. Approximately 4 portions each containing 10 mol% of sodium ascorbate and 5.5 mol% of $CuSO_4{\cdot}5H_2O$ were added in intervals of 30 minutes. Reactions were monitored using HPLC and TLC and usually took less than 4 hours to be completed. The reaction mixture was then neutralized by addition of solid $NaHCO_3$ and evaporated. Standard chromatographic purification on silica gel provided compounds **6a-d** in 35–45% isolated yields.

If amount of added sodium ascorbate exceeded 10 mol%, the formation of fluorescent amines **7** was observed. Amine **7b** was isolated in 13% yield.

Investigation of reactions of bistriazolylpurine deoxynucleosides **6** with amines to obtain fluorescent nucleosides is in progress.



6a R = phenyl, 36%	**7a** R = phenyl, 2%
6b R = butyl, 35%	**7b** R = butyl, 13%
6c R = pentyl, 45%	**7c** R = pentyl, 4%
6d R = 1-hydroxy-1-methylethyl, 36%	**7d** R = 1-hydroxy-1-methylethyl, 2%

Scheme 2. Diazide reactions with alkynes. Reagents and conditions: $CuSO_4{\cdot}5H_2O$, sodium ascorbate, acetic acid, *t*-BuOH/H_2O, r.t., 4 h

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REFERENCES

[1] Amblard, F.; Cho, J. H.; Schinazi, R. F. *Chem. Rev.* **2009**, *109*, 4207 and references cited therein.
[2] Kovaļovs, A.; Novosjolova, I.; Bizdēna, Ē.; Bižāne, I.; Skardziute, L.; Kazlauskas, K.; Jursenas, S.; Turks, M. *Tetrahedron Lett.* **2013**, *54*, 850.
[3] Nandanan, E.; Camaioni, E.; Jang, S.; Kim, Y.; Cristalli, G.; Herdewijn, P.; Secrist, J.; Tiwari, K.; Mohanram, A.; Harden T; Boyer J.; Jacobson K. et al. *J. Med. Chem.* **1999**, *42*, 1625.
[4] Robins, J. M.; Janeba, Z.; Francom, P. Method for the preparation of 2-halo-2’-deoxyadenosine compounds from 2’-deoxyguanosine. U.S. Pat. Appl. 2009/0270604 A1, 02.07.2009.