[P1.147]

Regioselective nucleophilic aromatic substitution of 2,6-bis-(1,2,3-triazolyl)-purine derivatives with various nucleophiles

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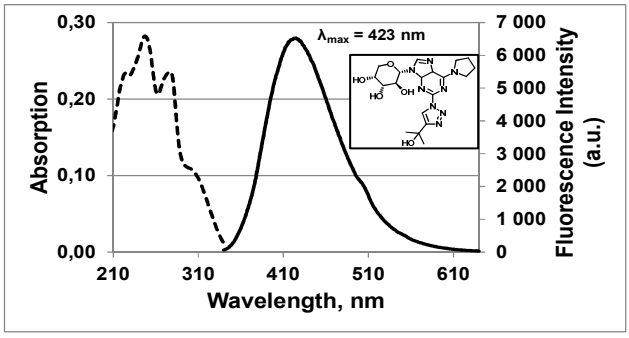
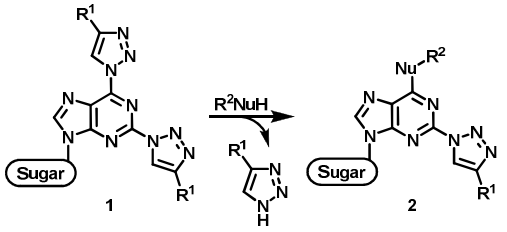
Recently, we have reported the synthesis and application of 2,6-bis-(1,2,3-triazol-1-yl)purine nucleosides **1** [1]. The 1,2,3-triazolyl group at C(6) position of purine has been shown to be a good leaving group in nucleophilic aromatic substitution reactions. In this study, we have extended the range of nucleophiles.

N-Nucleophiles such as methylamine, dimethylamine, pyrrolidine and piperidine were successfully used in substitution reactions and gave products **2** in good to excellent yields. For example, the S_NAr reactions between 9-(2',3',4'-tri-*O*-acetyl-α-D-arabinopyranosyl)-2,6-bis-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-9*H*-purine and amines proceed with yields up to 91%. THF or THF/H_2O were used as a solvent. Reaction temperatures varied from 20 till 40 ^oC and the time - from 30 min till 4 hours.

The absorption and emission spectra of products containing 6-amino-2-triazolylpurine group were studied in THF, MeCN, DMSO and water. A representative example of absorption (dashed line) and emission (solid line) spectra is given for 9-(α-D-arabinopyranosyl)-2-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-trizol-1-yl)-6-(pyrrolidin-1-yl)-9*H*-purine ($1.59•10^{-5}$ M) in MeOH:





Further, triphenylmethyl mercaptan, thiophenol, dodecanthiol, benzylthiol, propane-1,3-dithiol, decane-1,10-dithiol were used for the substitution. Thus, *S*-trityl protected 2-triazolyl-6-thiopurine derivative was obtained in reaction of 9-(2',3',5'-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-9*H*-purine with triphenyl-methyl mercaptan in 80% yield. Reactions of the same bis-triazolyl starting material with thiophenol and dodecanethiol proceed equally smoothly in DMF in the presence of K_2CO_3. After deacetylation of sugar moiety with $MeNH_2/H_2O$ target compounds were isolated in 82% and 62% yield.

In conclusion, a novel class of bis-triazolyl purine nucleosides were obtained from 2,6-diazido precursors via copper (I) catalyzed azide-alkyne cycloaddition. These intermediates appeared to be very reactive towards *N*- and *S*-nucleophiles and thus selectively gave C(6)-substituted analogs with triazolyl moiety at C(2)-position. The obtained 2-triazolyl purine derivatives exhibit interesting fluorescence properties.

References:

1. Kovaļovs, A.; Novosjolova, I.; Bizdēna, Ē.; Bižāne, I.; Skardziute, L.; Kazlauskas, K.; Jursenas, S.; Turks, M. *Tetrahedron Lett*. **2013**, *54*, 850.

Keywords: purine, 2,6-bistriazolyl derivative, 1,3-dipolar cycloaddition, fluorescence