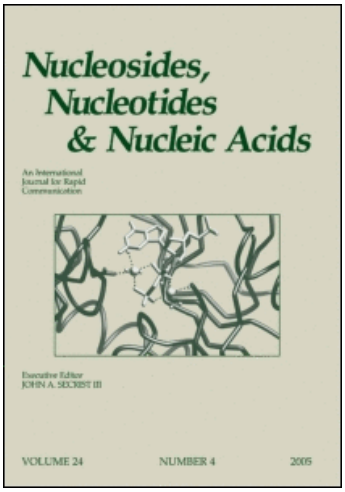


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Functionalization of Pyrimidine and Purine Nucleosides at C4 and C6: C-Nucleophilic Substitution of Their C4- and C6-(1,2,4-Triazol-1-yl) Derivatives

Victor Timoshchuk[a]
[a] TriLink BioTechnologies Inc., San Diego, California, USA

To cite this Article Timoshchuk, Victor(2005) 'Functionalization of Pyrimidine and Purine Nucleosides at C4 and C6: C-Nucleophilic Substitution of Their C4- and C6-(1,2,4-Triazol-1-yl) Derivatives', Nucleosides, Nucleotides and Nucleic Acids, 24: 5, 1043 — 1046
To link to this Article: DOI: 10.1081/NCN-200059763
URL: http://dx.doi.org/10.1081/NCN-200059763

Nucleosides, Nucleotides, and Nucleic Acids, 24 (5–7):1043–1046, (2005)

ISSN: 1525-7770 print/ 1532-2335 online
DOI: 10.1081/NCN-200059763

Taylor & Francis
Taylor & Francis Group

FUNCTIONALIZATION OF PYRIMIDINE AND PURINE NUCLEOSIDES AT C4 AND C6: C-NUCLEOPHILIC SUBSTITUTION OF THEIR C4- AND C6-(1,2,4-TRIAZOL-1-YL) DERIVATIVES

Victor Timoshchuk ▫ *TriLink BioTechnologies Inc., San Diego, California, USA*

▫ *A study of C-nucleophilic substitution at the C4-position on pyrimidine and C6-position on 2′-deoxyguanosine to produce novel nucleosides is presented with the spectroscopic properties of their respective substitution products. C4-(1,2,4-triazol-1-yl) pyrimidine nucleosides* **1** *were treated with nitroalkanes, malononitrile, acetylacetone, ethyl nitroacetate, acetoacetate and cyanoacetate at 100°C in dioxane in the presence of DBU resulting in the production of novel nucleosides* **2–11**. *To explore the application of this methodology to purine chemistry, this approach was used to produce novel analogs from 2′-deoxyguanosine. We found that the triazolo derivative* **12** *undergoes C-nucleophilic substitution with nitromethane, malononitrile, acetylacetone, ethyl nitroacetate and cyanoacetate in the presence of potassium carbonate (K_2CO_3) in DMF at 100°C to give novel nucleosides* **13–17**.

INTRODUCTION

The synthesis of pyrimidine and purine nucleosides modified at the C4 and C6 positions respectively is of considerable interest, particularly their potential biological effects. Several publications demonstrate that pyrimidine nucleosides properly activated at the C4-positions are easily transformed into numerous derivatives by S_NAr displacement. Efficient substitution with nitrogen, oxygen, and sulfur based nucleophiles occurs when the activating group on the nucleoside is a (1,2,4-triazol-1-yl),[1–7] arylsulfonyl,[8–12] or (imidazol-1-yl).[13]

Surprisingly there are no publications about C-4 displacement of pyrimidines with C-nucleophiles thus activated. Nor are there publications describing the modification of 2′-deoxyguanosine using this approach with any nucleophile. This paper presents our initial results on the use of C-nucleophiles with (1,2,4-triazol-1-yl) activated pyrimidine nucleosides and 2′-deoxyguanosine.

Address correspondence to Victor Timoshchuk, TriLink BioTechnologies Inc., San Diego, CA, USA; E-mail: vtimoshchuk@trilinkbiotech.com

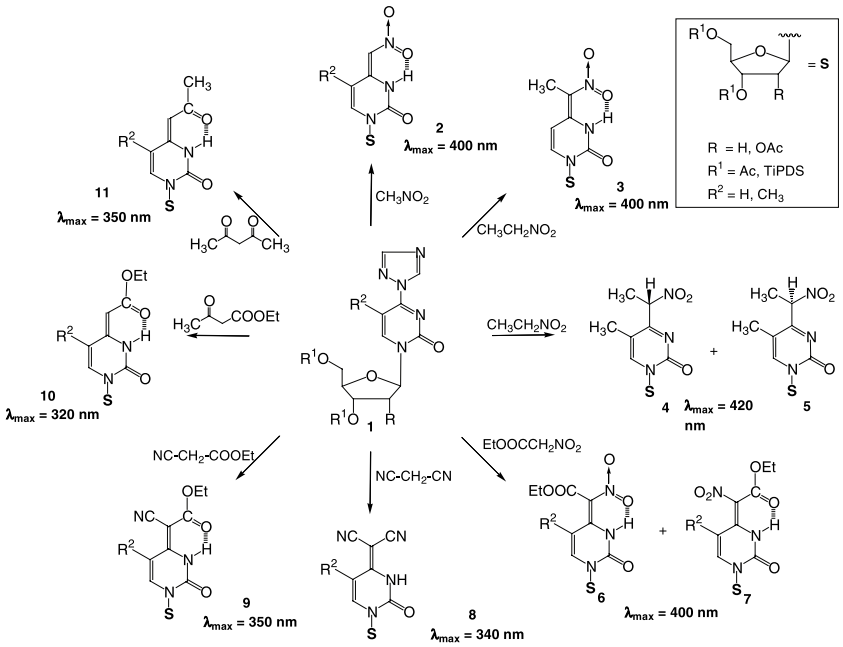
Pyrimidine Modification

The 4-(1,2,4-triazol-1-yl) derivatives of 3′,5′-di-O-acetyl-2′-deoxyuridine, 2′,3′,5′-tri-O-acetyluridine, 3′,5′-di-O-acetylthymidine and 3′,5′-O-(tetraisopropyl-disiloxanyl) thymidine were chosen as starting materials for the C-nucleophilic reactions shown in Scheme 1.

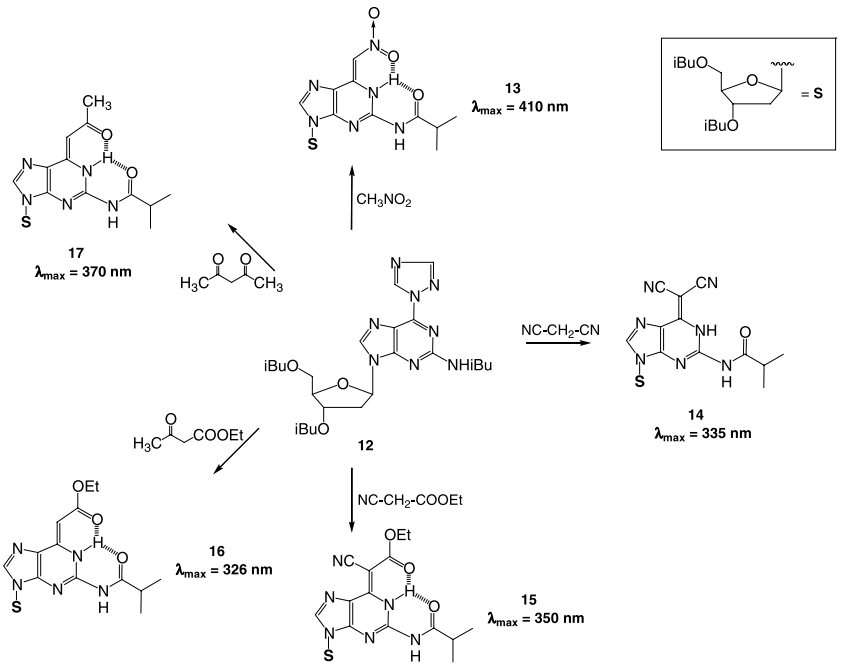
Solutions in dioxane were heated at 100°C with nitromethane in the presence of DBU (1 eq.) to give 4-nitroolefinic nucleosides **2**. The presence of two singlets for the NH and olefinic protons in the NMR spectra is strong evidence of these structures. The formation of only one of two possible isomers suggests strong stabilization by an intramolecular hydrogen bond, and is known to occur with other β-amino derivatives of nitroolefins.[14]

The reaction between triazolo derivatives of uridine and nitroethane gave only one isomer **3**. In the case of thymidine, two separate isomers **4** and **5** were formed with a ketimine structure, confirmed by NMR. The 5-methyl group in thymidine causes steric hindrance in the enamine form, resulting in the formation of the preferable ketimino structure. The treatment of nucleosides **1** with ethyl nitroacetate afforded the mixture of two isomers **6** and **7** with a slight prevalence of **6**.

4-Dicyanomethylene nucleosides **8** were formed in the reaction of **1** with malononitrile. The heating of **1** and ethyl cyanoacetate yielded nucleosides **9**.



SCHEME 1 The substitution of 4-(1,2,4-triazol-1-yl)pyrimidine nucleosides with compounds possessing an active methylene group.



SCHEME 2 The substitution of 6-(1,2,4-triazol-1-yl)purine nucleosides with compounds possessing an active methylene group.

The interactions of **1** with ethyl acetoacetate and acetylacetone gave compounds **10** and **11** as the sole isomers as expected from the cleavage of β-ketoesters and β-diketones.

2′-Deoxyguanosine Modification

The 6-(1,2,4-Triazol-1-yl) derivative of fully protected 2′-deoxyguanosine **12** did not react with C-nucleophiles when dioxane was used as the solvent under the conditions described for the pyrimidine modifications. However, the reactions occurred readily when carried out in DMF at 100°C in the presence of potassium carbonate. Compounds **13 17** were obtained by this very efficient method as shown in Scheme 2. Their structures were confirmed by NMR and UV spectra.

These nucleosides were deprotected by treatment with TBAF or methanolic ammonia without any visible decomposition. Strong acids and bases are not suitable for deprotecting these compounds as β-aminonitroolefinic compounds are easily destroyed by them.[14]

CONCLUSION

C-nucleophilic substitution of C4-(1,2,4-triazol-1-yl) pyrimidine and C6-(1,2,4-triazol-1-yl) 2′deoxyguanosine nucleosides was found to be an efficient method for

the synthesis of these novel derivatives. These analogs possess characteristic long wavelength absorbance at 350–420 nm as a result of the enamine structure which is stabilized by an intramolecular hydrogen bond, suggesting a potential application as fluorescent nucleosides.

We observed stereoselectivity of C-nucleophilic replacement in most cases. This can be attributed to the formation of a hydrogen-bound chelate, similar to that found in β-diketones. All synthesized nucleosides are stable in the presence of acetic acid, ammonia and TBAF. Conversely, they are destroyed easily by strong acids and bases, acyl chlorides, and reducing agents (Zn/AcOH, NaBH4, [H]/Pd/C).

REFERENCES

1. Reese, C.B.; Ubasawa, A. Tetrahedron Lett. **1980**, *21*, 2265–2268.
2. Divakar, K.J.; Reese, C.B. J. Chem. Soc., Perkin Trans., I **1982**, 1171–1176.
3. Sung, W.L. J. Org. Chem. **1982**, *47*, 3623–3628.
4. Adamiak, R.W.; Biala, E.; Gdaniec, Z.; Mielewczyk, S.; Skalski, B. Chem. Scr. **1982**, *26*, 3–6.
5. Hodge, R.P.; Brush, C.K.; Harris, C.M.; Harris, T.M. J. Org. Chem. **1991**, *56*, 1553–1564.
6. Kamaike, K.; Takahashi, M.; Utsugi, K.; Tomizuka, K.; Ishido, Y. Tetrahedron Lett. **1991**, *36*, 91–94.
7. Kamaike, K.; Takahashi, M.; Utsugi, K.; Tomizuka, K.; Okazaki, Y.; Tamada, Y.; Kinoshita, K.; Masuda, H.; Ishido, Y. Nucleosides Nucleotides **1996**, *15*, 749–769.
8. Zhou, X.-X.; Welch, C.J.; Chattopadhyaya, J. Acta Chem. Scand. **1986**, *B40*, 806–816.
9. Zhou, X.-X.; Chattopadhyaya, J. Tetrahedron **1986**, *42*, 5149–5156.
10. Sekine, M. J. Org. Chem. **1989**, *54*, 2321–2326.
11. Matsuda, A.; Yasuoka, J.; Sasaki, T.; Ueda, T. J. Med. Chem. **1991**, *34*, 999–1002.
12. Komatsu, H.; Morizane, K.; Kohno, T.; Tanikawa, H. Org. Process Res. Dev. **2004**, *8*, 564–567.
13. Lin, X.; Robins, M.J. Org. Lett. **2000**, *2*, 3497–3499.
14. Freeman, J.P.; Emmons, W.D. J. Am. Chem. Soc. **1956**, *78*, 3405–3408.