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Highly regioselective 1,3-dipolar cycloaddition of 3′-*O*-propargyl guanosine with nitrile oxide: An efficient method for the synthesis of guanosine containing isoxazole moiety

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ABSTRACT

The 1,3-dipolar cycloaddition reaction of 3′-*O*-propargyl guanosine with various *in-situ* generated nitrile oxides in the presence of DMF as a solvent is described. It is noteworthy that the reaction is highly regioselective that affords biologically important guanosine containing isoxazole moiety in good yields with high purities.

The nucleic acid chemistry has been the subject of immense interest in the area of medicinal chemistry as the nucleotides serve as a versatile building blocks for both DNA and RNA synthesis as well as involve in numerous critical biological process [1,2]. It has been well documented in the literature that there are several approved drugs on the market containing nucleoside/nucleotide analogs have been used for the treatment of cancers, parasites, bacterial, viral and fungal infections [3,4]. Notably, these analogs represent the unique class of antiviral drugs for various viruses such as human immunodeficiency virus (HIV), hepatitis C virus (HCV), influenza virus, respiratory syncytial virus (RSV), hepatitis B virus (HBV), human papillomavirus (HPV), human cytomegalovirus (HCMV), herpes simplex virus (HSV), and varicella-zoster virus (VZV) [5]. It is believed that nucleoside analog acts as a prodrug which converts into the corresponding triphosphorylated analog in the presence of kinase. The active form of the drug is the triphosphorylated analog that acts as an inhibitor for intracellular enzymes and helps to inhibit the viral replication. The chemical modifications in the sugar moiety has had a great impact in terms of biological activity as well as degree of selective toxicity. Given the global pandemic due to the outbreak of the novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) and also the emerging infectious diseases worldwide from several other viruses [6,7], the development of novel antiviral drugs containing nucleoside/nucleotide analogs with a broad spectrum activity against different virus genotypes or viral strains has been warranted.

The 1,3-dipolar cycloaddition provides a powerful method for the construction of novel heterocyclic compounds [8]. In particular, the 1,3-dipolar cycloaddition of alkynes with nitrile oxide results in the formation of biologically important isoxazole derivatives [9]. It is to be noted that several approved drugs with isoxazole derivatives display several therapeutic activities such as antibacterial, antifungal, antitubercular, antipsychotic, antitumor, antidepressant, antirheumatic, anticonvulsant, and bronchodilatory agent [10]. While the 1,3-dipolarcycloaddition reaction with nitrile oxide involving pyrimidine nucleosides have been studied [11–15], to the best of our knowledge, no example of 1,3-dipolarcycloaddition reaction with nitrile oxide involving guanosine nucleoside has been reported in the literature. It has been reported that several 2′-deoxyuridine containing isoxazole derivatives display antiviral activity against HSV and several RNA viruses [13]. In addition, these analogs exhibit activities against several types of human cancer cell lines [14]. Furthermore, Guo *et al.* reported that several 5-isoxazol-3-yl-pyrimidine nucleosides exhibited significant *in vitro* antileishmanial activity [15]. We envisaged that the design of new guanosine containing isoxazole moiety may possess potentially interesting biological activity for various therapeutical applications such as antiviral, anticancer, and antileishmanial agents. Our continuous interest in the area of nucleic acid chemistry [16], prompted us to synthesize guanosine containing isoxazole

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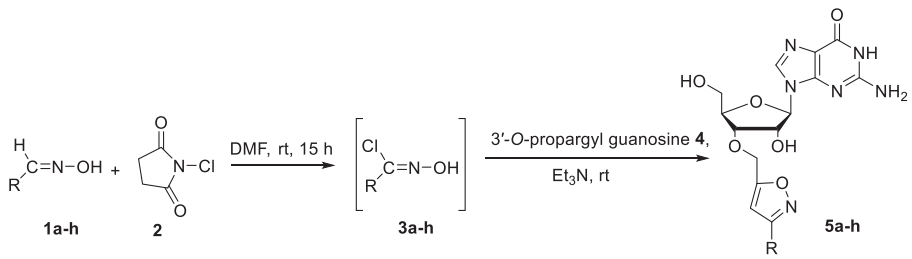

Scheme 1. 1,3-Dipolar cycloaddition of 3′-*O*-propargyl guanosine **4** with nitrile oxide.

moiety and study its biolgical evaluation. Herein, we report the first example of the 1,3-dipolar cycloaddition of 3′-*O*-propargyl guanosine with nitrile oxides, leading to the formation of guanosine containing isoxazole moiety in good yields with high purities.

Treatment of benzaldehyde oxime (**1a**) with *N*-chlorosuccinimide (**2**) in the presence of DMF as a solvent, followed by the reaction with 3′-*O*-propargyl guanosine (**4**) using triethylamine as a base gave guanosine containing isoxazole moiety **5a** in 84% yield (Scheme 1). The overall reaction involves the generation of *N*-benzhydroxyiminoyl chloride (**3a**), followed by the *in-situ* formation of the corresponding nitrile oxide and subsequent 1,3-dipolar cycloaddition to afford the final product, guanosine containing isoxazole moiety **5a**. The 1,3-dipolar cycloaddition is highly regioselective affording exclusive 3,5-disubstituted isoxazole **5a**. The structure of **5a** was ascertained by ^{1}H and ^{13}C NMR and mass spectral data [17]. The regiochemistry of **5a** was unequivocally established by typical NOESY NMR techniques. The data show that there is no nuclear overhauser effect (NOE) signal between one of the C5 adjacent methylene protons and ortho proton of the phenyl ring present in the isoxazole moiety (Fig. 1). The other possible 3,4-disubstituted regioisomer **6a** was not detected in the ^{1}H NMR spectrum of the crude reaction mixture (Fig. 2).

Table 1 delineates the results obtained for the reaction of 3′-*O*-propargyl guanosine (**4**) with various oximes **1a-h**. Aryl oximes with an electron-withdrawing or an electron-donating group on the aromatic ring react efficiently with **4** under optimized conditions afforded the corresponding guanosine containing isoxazole moieties **5b-d** in good yields indicating that this cycloaddition reaction is insensitive to electronic effects (entries 2–4). Similarly, the addition is also insensitive to steric substituent. The reaction of **4** with 9-anthraldehyde oxime (**1e**) under similar conditions afforded the corresponding product **5e** in 72% yield (entry 5). Furthermore, the cycloaddition was successfully extended to heterocyclic oximes. Under similar conditions, the cycloaddition reaction of **4** with 3-pyridinealdoxime (**1f**), 4-bromo-2-thiophenecarbaldehyde oxime (**1g**), and 1*H*-indole-3-carboxaldehyde oxime (**1h**) afforded the corresponding products **5f-h** in 77%, 71%, and 79% yields, respectively (entries 6–8).

There are several interesting features that merit comments for the present 1,3-dipolar cycloaddition reaction. First, unlike conventional 1,3-dipolar cycloaddition reaction [8], the present reaction involves the *in-situ* generation of nitrile oxide from aldoxime without isolation and handling of potentially harmful and unstable hydroxyiminoyl chloride. Second, in all cases, the 1,3-dipolar cycloaddition is highly regioselective affording exclusive 3,5-disubstituted regioisomer **5** in good yields. Third, the purification procedure is simple and straightforward that involves pass through silica gel column furnishing final pure product **5** with extremely high purities based on HPLC (>99.5%). It is to be noted that high purity product is necessary for the successful biological applications. Fourth, several approved drugs on the market with nucleoside analogs have been used for the treatment of cancer,

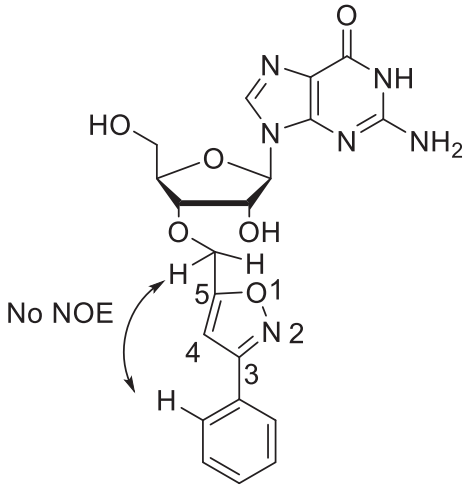

Fig. 1. Structure of 3,5-disubstituted regioisomer **5a.**

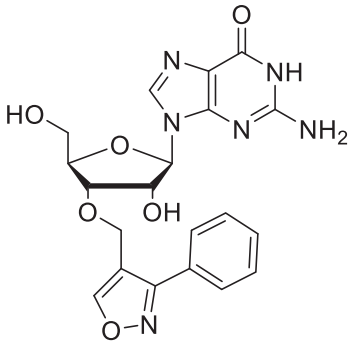

Fig. 2. Structure of 3,4-disubstituted regioisomer **6a.**

Table 1
Results of the 1,3-dipolar cycloaddition of 3′-*O*-propargyl guanosine with nitrile oxide.

Entry	Chloroxime	Reaction time (h)	Product	R	Yield[a] (%)
1	**3a**	24	**5a**	phenyl	84
2	**3b**	36	**5b**	4-methoy-phenyl	74
3	**3c**	48	**5c**	2-chloro-phenyl	70
4	**3d**	36	**5d**	4-nitro-phenyl	77
5	**3e**	60	**5e**	9-anthracyl	72
6	**3f**	48	**5f**	3-pyridyl	77
7	**3g**	60	**5g**	4-bromo-2-thiophenyl	71
8	**3h**	48	**5h**	3-indolyl	79

[a] Isolated yield of pure product.

bacterial and viral infections. Given the precedent in the literature, it is likely that the present guanosine containing isoxazole moiety can be a potential lead candidate in the field of medicinal chemistry.

In summary, we have developed the 1,3-dipolarcycloaddition reaction of 3′-*O*-propargyl guanosine with various nitrile oxides that allows an efficient synthesis of guanosine containing isoxazole moiety in good yields with high purities. The reaction is highly regioselective affording exclusive 3,5-disubstituted isoxazole. Further work is in progress to extend the scope of this reaction to triphosphate analogs and other purine bases and to study the biological applications of these new guanosine containing isoxazole moiety.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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[17] General procedure to make 5: To a stirred solution of aldoxime (2.0 mmol) in DMF (10.0 mL) at room temp., N-chlorosuccinimide (2.0 mmol) was added and the mixture was stirred for 15 h. After 15 h, triethylamine (2.0 mmol) and 3′-O-propargyl guanosine (1.0 mmol) were added to the reaction mixture and stirred for the time specified in Table 1. The reaction mixture was evaporated under rotary evaporator to give crude reaction mixture. The crude reaction mixture was purified by silica gel column chromatography using Biotage instrument (DCM/MeOH, 9:1). The fractions containing the pure product were evaporated and dried to give a solid 5. Data for 5a: 1H NMR (DMSO-d6, 400 MHz) δ 10.65 (bs, 1H), 7.96 (s, 1H), 7.89 (m, 2H), 7.53 (m, 3H), 7.10 (s, 1H), 6.48 (bs, 2H), 5.75 (d, J = 6.8 Hz, 1H), 4.96 (d, J = 13.6 Hz, 1H), 4.85 (d, J = 13.6 Hz, 1H), 4.66 (m, 1H), 4.15 (m, 1H), 4.05 (m, 1H), 3.60 (m, 2H); 13C NMR (DMSO-d6, 162 MHz) δ 170.59, 162.29, 157.16, 154.21, 151.89, 135.91, 130.75, 129.63, 128.95, 127.09, 117.08, 102.03, 86.43, 83.65, 79.24, 73.62, 63.06, 61.77; MS (m/z): 439 [M-H]-.