1,2,3-Triazoles as leaving groups: S\textsubscript{N}Ar reactions of 2,6-bistriazolylpurines with O- and C-nucleophiles

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Abstract
A new approach was designed for the synthesis of C6-substituted 2-triazolylpurine derivatives. A series of substituted products was obtained in S\textsubscript{N}Ar reactions between 2,6-bistriazolylpurine derivatives and O- and C-nucleophiles under mild conditions. The products were isolated in yields up to 87%. The developed C–O and C–C bond forming reactions clearly show the ability of the 1,2,3-triazolyl ring at the C6 position of purine to act as leaving group.

Introduction
Modified purine derivatives are an important class of compounds which possess a wide spectrum of biological activities [1-6]. They are often used as antiviral, anticancer and antibacterial agents. Such intensive medicinal chemistry applications demand for constant development of novel synthetic methodologies. Frequently, the purine structure is modified in S\textsubscript{N}Ar reactions with N- [7-11] and S-nucleophiles [12-14] and in metal catalyzed reactions of halopurine derivatives [15-20]. Modifications of purines with O-nucleophiles are based on S\textsubscript{N}Ar reactions between 6-halopurine derivatives and alcohols [21-28] in the presence of a base. Alcohols are used in excess (5–40 equiv) and often play a role of both solvent and reagent. Reactions usually are performed in polar aprotic solvents such as DMF, MeCN or THF using alkoxides NaH, K\textsubscript{2}CO\textsubscript{3} or Na\textsubscript{2}CO\textsubscript{3} as a base, respectively.

Other methods for the introduction of alkylxy or aryloxy substituents in the purine structure involve substitution reactions of different leaving groups such as: 1) benzotriazolylxy group (HOBT) [8,29-32]; 2) the alkylimidazolyl group [33,34] and 3) in-situ-generated alkylammonia salts [35-38]. In 1995, the Robins group demonstrated S\textsubscript{N}Ar reactions of 6-(1,2,4-triazol-4-yl)purine with dimethylamine, sodium methoxide and sodium thiourea [39]. Earlier, the use of 6-(1,2,4-triazol-1-yl)purine derivatives in S\textsubscript{N}Ar reactions has been reported [40]. An alternative method for the synthesis of
Azolylpurine derivatives are important due to their potential as drug candidates. They can be used as agonists and antagonists of adenosine receptors [58,64-66] and against Mycobacterium tuberculosis [60]. They also show useful fluorescent properties [11,67-69] and can be used as metal ion sensors [70]. Therefore, it is important to develop novel methods towards this type of derivatives. To date two approaches have been used to obtain 6-substituted 2-triazolylpurine derivatives (Scheme 1). According to the pathway A, firstly a selected substituent is introduced at the C6 position of the purine ring using SNAr reactions (Ia→II, Scheme 1). If purine contains identical leaving groups at C2 and C6 positions the reactivity order in its SNAr reactions is C6 > C2 [71,72]. Also transition metal catalyzed reactions can be used for C6 functionalization of purine [73-76] or alkylation of inosine or guanosine derivatives (Ib→II, Scheme 1) [30,36]. In the next step, azide can be introduced either by a second SNAr reaction on the C2-halo derivative or by diazotization/azidation at C2. Then, the Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reaction provides the target product IV (Scheme 1, pathway A) [59-61]. Pathway B is designed on the basis of our group investigations on the synthesis of 2,6-bistriazolylpurine derivatives and their application in reactions with N-, S- and P-nucleophiles making use of regioselective SNAr reactions at C(6) (V→VI→IV, Scheme 1) [11,14,62,63,77,78]. The main advantage of pathway B is a straightforward access to 2,6-diazidopurines V and 2,6-bistriazolylpurines VI due to excellent nucleophilic properties of the azide ion and well-established CuAAC reaction. Pathway B also avoids performing of an SNAr process on partially deactivated purines as the introduced nucleophiles are mostly seen as electron-donating substituents (e.g., R2N-, RS-, RO-).

Herein, we report a synthetic extension of this methodology. We have found that the pronounced leaving group character of 1,2,3-triazoles makes 2,6-bistriazolylpurines excellent substrates for SNAr reactions with O- and C-nucleophiles.

\[
\text{Scheme 1: Synthetic pathways for the synthesis of 6-substituted 2-triazolylpurine derivatives IV.}
\]
Results and Discussion

Synthesis of 2,6-bistriazolylpurine derivatives and their reactions with O-nucleophiles

The 2,6-diazidopurine derivatives 1a and 1b as strategic starting materials and 2,6-bistriazolylpurine derivatives 2a–c were obtained in the synthetic procedures developed by us before [11,14,67]. The CuAAC reaction was performed between diazide derivatives 1a and 1b and phenylacetylene or methyl propiolate (Scheme 2).

\[ \text{R}^2 \equiv \text{CuSO}_4 \cdot 5\text{H}_2\text{O} \]
\[ \text{C}_6\text{H}_5\text{NaO}_3 \]
\[ \text{F-BuOH} \]
\[ \text{AcOH/H}_2\text{O} \]

\[ \text{2a: } \text{R}^2 = \text{COOMe, 45\%} \]
\[ \text{2b: } \text{R}^2 = \text{Ph, 77\%} \]

\[ \text{1a: } \text{R}^1 = \text{Ac-O-ribofuranosyl} \]
\[ \text{1b: } \text{R}^1 = \text{n-C}_7\text{H}_{15} \]

\[ \text{2c, 75\%} \]

\[ \text{Scheme 2: Synthesis of 2,6-bistriazolylpurine derivatives 2a–c.} \]

SnAr reactions between bistriazolylpurine derivatives and O-nucleophiles were first performed on N9-alkylated bistriazole 2c. The reactions were carried out with primary and secondary alcohols in the presence of NaH in DMF. The developed transformation required only nearly equimolar loading of an alcohol and a base, and products 3a–f were obtained in yields up to 83\% (Scheme 3). In most cases the full conversion of the starting material was reached in 15–30 min at room temperature, which clearly showed the excellent leaving group ability of the triazolyl ring. These SnAr reactions can also be performed in DMSO or DMF in the presence of K$_2$CO$_3$, but the

\[ \text{ROH (1.3 equiv), NaH (1.1 equiv)} \]
\[ \text{DMF} \]

\[ \text{3a, 83\%} \]
\[ \text{3b, 79\%} \]
\[ \text{3c, 43\%} \]

\[ \text{3d, 76\%} \]
\[ \text{3e, 80\%} \]
\[ \text{3f, 82\%} \]

\[ \text{Scheme 3: Synthesis of 6-alkyloxy-2-triazolylpurine derivatives 3a–f.} \]
completion of these transformations requires heating the reaction mixtures up to 60 °C for 24 h.

An SNAr reaction with a non-trivial alcohol was demonstrated on the example of 2',3'-O-isopropylideneuridine and product 3f was isolated after 21 h of heating at 50 °C in 82% yield. It should be noted that tertiary alcohols (e.g., t-BuOH) were inert in SNAr reactions with 2,6-bistriazolylpurines and their attempted reactions resulted in an unidentifiable mixture of by-products.

The following experiments were performed on 2,6-bistriazolylpurine nucleoside 2b in MeOH, EtOH and PrOH used as solvents and nucleophiles in the presence of NaH (5.0 equiv). The excess of base and alcohol was required due to the cleavage of acetyl protecting groups. Products 3g–i were obtained in yields of up to 79% (Scheme 4). Furthermore, purification of the products 3g–i was complicated due to their poor solubility in organic solvents. The C6 regioselectivity of SNAr reactions was proved by 13C NMR comparison of the products 3a–i with similar compounds from literature [61].

Intriguingly, we were able to conserve the acetate protecting groups in product 3j, when the SNAr reaction was performed in the presence of DBU used as base. The artificial dinucleotide analogue 3j was obtained in 25% isolated yield.

We have explored also reactions of 2,6-bistriazolylpurines 2a and 2c with water in buffered and basic medium, respectively (Scheme 5). The buffered conditions (NaOAc/DMSO/H2O)
were sufficiently mild to maintain the acetyl protecting groups in product 4a. Also hydrolysis of 2c into 4b proceeded under mild conditions and only gentle warming to 50 °C was required.

2,6-Bistriazolylpurine derivatives in S_N_Ar reactions with C-nucleophiles

Next, S_N_Ar reactions between 2,6-bistriazolylpurine 2c and C-nucleophiles offered an easy way for the C–N bond transformation into a C–C bond. Compounds containing electron-withdrawing groups such as malonitrile, dimeredone, ethyl cyanoacetate and diethyl malonate were used as C-nucleophiles. Transformations were performed in DMF in the presence of NaH and the products were obtained in high yields (Scheme 6). The lower yield of compound 5d was obtained due to the ethyl ester hydrolysis and subsequent decarboxylation. Such side reactions were also observed for similar compounds in literature [79,80].

As a limitation of the method we have found that 2,6-bistriazolylpurine 2c was inert to S_N_Ar reactions with deprotonated acetylacetone and diphenylmethane. Even there are reports on S_N_Ar reactions of acetylacetone with purines and pyrimidines [56,80], in our hands only polymerization of acetylacetone was observed. On the other hand, the diphenylmethane anion (pK_a 32; DMSO [81]) apparently is too basic and deprotonates purine C(8)–H, thus suspending the S_N_Ar process.

The structures of C6-substituted products 5a–d were elucidated by NMR and IR analysis. These compounds can exist as either C–H acids (A) or N–H acids (B), but dimeredone conjugate 5b may possess also an enol form C (Figure 1). During the structural studies of cyano group containing products 5a and 5c the cross signals for the C(2'')–H system were not found using HSQC spectra, excluding the existence of C–H tautomeric forms A. In addition, IR analysis (KBr tablet) indicated absorption bands of cyano groups at 2205 and 2170 cm⁻¹ for product 5a and at 2205 cm⁻¹ for product 5c. These results differ from the absorption in the range of 2260–2240 cm⁻¹, which would be characteristic for a cyano group attached to sp³-hybridized carbon [82]. On the other hand, 13C NMR shifts of the C(2'') position of purine–malononitrile conjugate 5a and ethyl cyanoacetate–purine conjugate 5c were 40.9 and 61.7 ppm, respectively. This range does not fully correspond to the theoretical values 80–140 ppm, expected for the Csp² atom of the N–H form B. In compound 5e the N–H form 5cB is possibly the major tautomer in CDCl₃ solution as it is stabilized via an intramolecular hydrogen bond. This is supported by a smaller deviation of the C(2'') chemical shift value (61.7 ppm) in comparison to the theoretical shifts for a Csp³ centre. Similar structural analogues are known in the literature [54,83-85] but their structural analysis was incomplete. As the aforementioned experiments did not determine preference for tautomer A or B of compound 5a, it was analysed in its deprotonated form C (CD₃OD/D₂O/NaOD). Interestingly, that the 13C NMR spectrum of 5a in basic medium revealed a similar chemical shift for carbon C(2'') (40.9 ppm) as in neutral CD₃OD.

The 13C NMR analysis of purine–dimedone conjugate 5b revealed two downfield shifts of 194.1 and 185.3 ppm. It showed that the structure is not symmetrical and corresponds to either tautomer structure B or C in CDCl₃ solution with a theo-
retirical preference for enol form C. Finally, the structure of C–H
tautomer 5dA was proved by its HSQC spectrum, in which a
cross peak clearly indicated the C(2'')–H system.

Conclusion
The S_NAr reactivity of 2,6-bis(1,2,3-triazol-1-yl)purine deriva-
tives was extended with their substitution with O- and
C-nucleophiles. The reactions proceeded under transition metal
free conditions and revealed excellent C6 selectivity. The de-
veloped synthetic approach provided O-adducts with 25–83%
yields and C-adducts with 67–87% yields. The methodology
demonstrated the leaving group ability of the 1,2,3-triazolyl
substituent at the C6 position of the purine ring.

Experimental
General information
^1H and ^13C NMR spectra were recorded with a Bruker Avance
300 or a Bruker Avance 500 spectrometer, at 300 and 75.5 MHz
or 500 and 125.7 MHz, respectively. The proton signals for
residual non-deuterated solvents (δ 7.26 for CDCl_3, δ 2.50 for
DMSO-d_6, δ 3.31 for CD_3OD) and the carbon signals (δ 77.1
for CDCl_3, δ 39.5 for DMSO-d_6, δ 49.0 for CD_3OD) were used
as an internal reference for ^1H and ^13C NMR spectra, respec-
tively. Coupling constants are reported in Hz. Chemical shifts
of signals are given in ppm and multiplicities are assigned as
follows: s – singlet, d – doublet, t – triplet, m – multiplet, brs –
broad singlet, tq – triplet of quartets.
Analytical thin-layer chromatography (TLC) was performed on Merck 60 Å silica gel F254 plates. Column chromatography was performed on Merck 40–60 μm 60 Å silica gel. Yields of products refer to chromatographically and spectroscopically homogeneous materials. The solvents used in the reactions were dried with standard drying agents and freshly distilled prior to use. Commercial reagents were used as received.

IR spectra were recorded in KBr tablets with a Perkin–Elmer Spectrum BX FTIR spectrometer (4000–450 cm⁻¹). Wavelengths are given in cm⁻¹.

For HPLC analysis an Agilent Technologies 1200 Series chromatograph equipped with an Agilent XDB-C18 (4.6 × 50 mm, 1.8 μm) column was used. Eluent A: 0.1% TFA solution with 5% v/v MeCN added; eluent B – MeCN. Gradient: 10–95% B 5 min, 95% B 5 min, 95–10% B 2 min. Flow: 1 mL/min. Wavelength of detection was 260 nm.

LC–MS was recorded with a Waters Acquity UPLC system equipped with Acquity UPLC BEH C18 1.7 μm, 2.1 × 50 mm; using 0.1% TFA/H₂O and MeCN for mobile phase. HRMS analyses were performed on an Agilent 1290 Infinity series UPLC system equipped with column Extend C18 RRHD 2.1 × 50 mm, 1.8 μm connected to an Agilent 6230 TOF LC/MS mass spectrometer.

General procedures and product characterization

Synthesis of compounds 1a,b and 2a–c and their characterization are described earlier [11,14,67].

Synthesis of 6-O-substituted 2-triazolylpurines
General procedure A for the S₄NAr reaction with O-nucleophiles

9-(β-D-Ribofuranosyl)-6-methoxy-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-9H-purine (3g): To a solution of 9-(2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)-2,6-bis(4-phenyl-1H-1,2,3-triazol-1-yl)-9H-purine (2b, 335 mg, 0.50 mmol, 1.0 equiv) in MeOH (6 mL) a suspension of NaH (60 mg, 2.52 mmol, 5.0 equiv) in MeOH (6 mL) was added and the reaction mixture was stirred for 10 min at rt, controlled by HPLC. Then AcOH (0.2 mL) was added and the mixture was partially evaporated. The suspension was centrifuged, the solids were separated and washed with MeOH (4 × 7 mL). Colourless solid. Yield 168 mg, 79%.

HPLC: tR = 4.20 min, purity 95%; IR (KBr) ν (cm⁻¹): 3390, 2950, 1605, 1490, 1455, 1400, 1365, 1245, 1035, 1020; ¹H NMR (300 MHz, DMSO-ᴅ₆ + D₂O) δ 9.38 (s, 1H, H-C(triazole)), 8.70 (s, 1H, H-C(8)), 8.02 (d, 3J = 7.6 Hz, 2H, Ar), 7.50 (t, 3J = 7.6 Hz, 2H, Ar), 7.39 (t, 3J = 7.6 Hz, 1H, Ar), 6.06 (d, 3J₁,₂ = 5.8 Hz, 1H, H-C(1’)), 4.65 (dd, 3J₂,₃ = 5.8 Hz, 3J₂,₄ = 4.8 Hz, 1H, H-C(2’)), 4.29 (s, 3H, -OCH₃), 4.22 (dd, 3J₃,₄ = 4.8 Hz, 3J₃,₅ = 3.7 Hz, 1H, H-C(3’)), 4.01 (dt, 3J₅,₆ = 3.7 Hz, 3J₄,₅,₆ = 3.5 Hz, 1H, H-C(4’)), 3.71 (dd, 3J₆,₇,₈ = 4.0 Hz, 3J₅,₆ = 12.1 Hz, 1H, Ha(5’)), 3.60 (dd, 3J₄,₅,₆ = 4.0 Hz, 3J₅,₆ = 12.1 Hz, 1H, Hb(5’)). ¹³C NMR (75.5 MHz, DMSO-ᴅ₆ + D₂O) δ 161.5, 152.8, 148.3, 147.5, 143.0, 130.1, 128.7, 128.3, 125.9, 120.6, 118.6, 69.8, 44.2, 31.5, 29.9, 28.6, 26.5, 22.4, 22.1, 13.9, 10.5; HRESIMS (m/z): [M + H]+ calcd for C₂₃H₂₂O₇N₆, 420.2506; found, 420.2510 (0.95 ppm).

General procedure B for the S₄NAr reaction with O-nucleophiles

Synthesis of C6-substituted 2-triazolylpurines
General procedure C for the S₄NAr reaction with C-nucleophiles

2-(9-Heptyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-1,9-dihydro-6H-purin-6-ylidene)malononitrile (5a): Under argon atmosphere to a suspension of 9-heptyl-2,6-bis(4-phenyl-1H-1,2,3-triazol-1-yl)-9H-purine (2c, 141 mg, 0.28 mmol, 1 equiv) in anhydrous DMF (2.5 mL) malononitrile (23 mg, 0.35 mmol,
The authors thank the Latvian Council of Science grant LZP-Funding 426.2149; found, 426.2149 (0 ppm). [M + H]$^+$: 242, 23.6, 14.3; HRESIMS ($^{13}$C), 1.31 (C(6')), 0.86 (t, $^2$J = 1.23 (m, 4H, H $^\text{-}2$C(3')), 1.96 (1H, H-C(8)), 7.94 (d, $^2$J = 7.5 Hz, 2H, Ar), 7.47 (d, $^2$J = 7.5 Hz, 2H, Ar), 7.37 (t, $^2$J = 7.5 Hz, 1H, Ar), 4.28 (t, $^3$J $^\text{H}^\text{-}2$C(3'), 1.40–1.32 (m, 4H, H$^\text{-}2$C(3'), H$^\text{-}2$C(2')), 1.31–1.23 (m, 4H, H$^\text{-}2$C(5'), H$^\text{-}2$C(6')), 0.86 (t, $^3$J = 6.9 Hz, 3H, H$^\text{-}2$C(7')); $^{13}$C NMR (75.5 MHz, CD$_2$OD) δ (ppm): 161.3, 150.4, 152.0, 148.7, 142.4, 131.4, 130.0, 129.5, 126.9, 125.2, 123.4, 120.7, 44.7, 40.9, 32.9, 31.2, 29.9, 27.6, 23.6, 14.3; HREIMS (m/z): [M + H]$^+$ calcd for C$_{23}$H$_24$N$_9$, 426.2149; found, 426.2149 (0 ppm).

Supporting Information
Supporting Information File 1
Full experimental procedures and copies of $^1$H, $^{13}$C and $^{15}$N HSQC NMR spectra.

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[Supplementary Material]
- Supporting Information: Detailed procedures and NMR spectra.

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