An Efficient Stereospecific Method for the Synthesis of 8-Aza-3-deazaguanine Nucleosides from Glycosyl Azides

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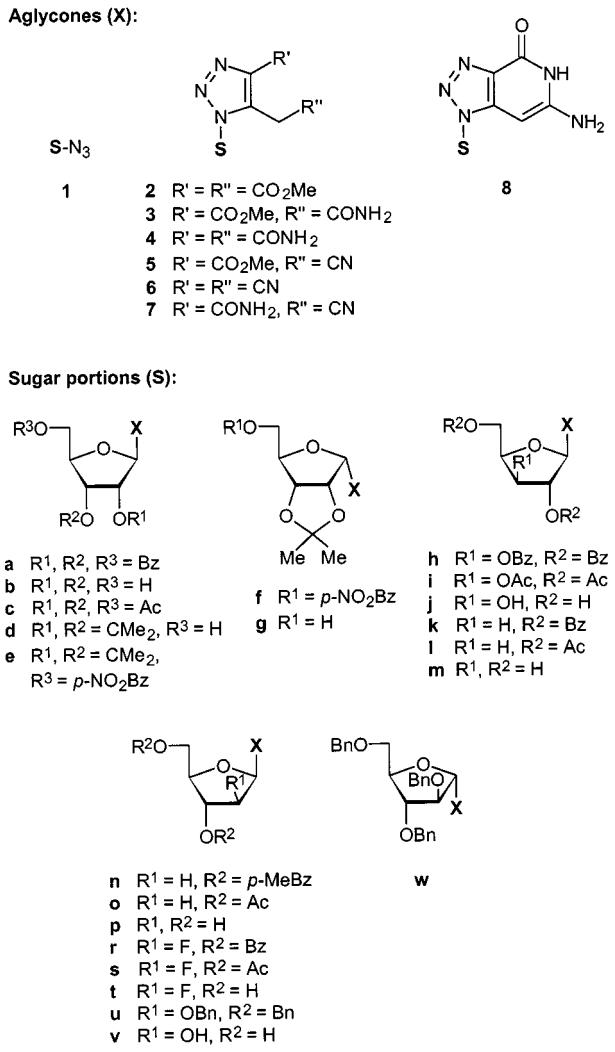
Abstract:8-aza-3-deazaguanine nucleosides **8** were prepared from glycosyl azides **1** via a stereospecific Dimroth reaction with dimethyl 3-oxoglutarate, followed by selective manipulation of the 1,2,3-triazole C-4 and 5 substituents. Of the two methods evaluated for the model synthesis of 8-aza-3-deazaguanosine, that involving selective dehydration of the diamides **4** and subsequent ring closure and deprotection of cyanoamides **7** afforded target nucleosides of superior purity.

Key words: glycosyl azides, Dimroth reaction, 1,2,3-triazoles, 1,2,3-triazolo[4,5-*c*]pyridines, nucleoside analogues

Several 8-aza- and 3-deazapurines as well as the appropriate nucleosides display interesting antiviral and antitumour activity.[2] However, little is known about the chemistry, and still less about the biological effects, of the hybrid 8-aza-3-deazapurine counterparts.[2,3] The replacement of 2'-deoxyguanosine by a 3-deaza modified building block within oligonucleotides results in a minor groove modification of the duplex and it possibly reduces its binding capacity.[4] However, the recently reported specific structure requirements for quadruplex-forming hexadeoxyribonucleotides with high anti-HIV-1 activity[5] suggested a more detailed investigation of the possible self-assembled 8-aza-3-deazaguanine nucleoside ionophore possessing appropriate donor-acceptor properties as the natural guanosine while lacking minor groove acceptor ability.[6] The synthesis of 8-aza-3-deazaguanosine (**8b**), the only known representative of the 1,2,3-triazolo[4,5-*c*]pyridine nucleoside analogue isosteric to guanine, has been previously prepared by the ammonolysis of the *O*-protected methyl 5-cyanomethyl-1-(β-D-ribofuranosyl)-1,2,3-triazole-4-carboxylate.[7-9] Although the cyclization proceeded almost quantitatively, the purification of the highly colored nucleoside led to a substantial loss of material (29-37% reported yields). The requisite precursor has been in turn prepared either directly via glycosylation of a suitable 1,2,3-triazole derivative (convergent approach)[7] or in few steps using linear methodologies.[8,9] In view of the poor regioselectivity of the glycosylation, linear approaches greatly improved the yield of the regioisomeric intermediates suitable for further conversion to **8b**. These include the 1,3-dipolar cycloaddition of the azide **1a** with methyl 4-hydroxy-2-butynoate[8] or dimethyl 1,3-allenedicarboxylate[9] as the key steps. Our method using dimethyl 1,3-allenedicarboxylate proved to be more efficient than the former since a dipolarophile with requisite number of C-atoms was utilized, however, it still suffered from slow reactivity of **1a** with the allenic ester as well as the high instability of the dipolarophile.

In continuation of our efforts in the synthesis of 8-aza-3-deazaguanine nucleosides with various glycosyl residues, retrosynthetic analysis suggested a more efficient approach to this class of compounds. The Dimroth reaction[10] of glycosyl azides **1**[11] with dimethyl 3-oxoglutarate (DOG), possessing the appropriate number of C-atoms, was expected to produce the desired regioisomers **2** exclusively. The Dimroth reaction usually requires strongly alkaline medium, however, the application to the base-sensitive glycosyl azides required some adaptation of the reaction conditions. In this regard, reaction of the azide **1a** with DOG in a K_2CO_3/DMSO system[12] provided the optimal conditions. The success of the reaction critically depended on the stoichiometry of the reactants. At the optimal molar ratio of **1a** : DOG : K_2CO_3 = 1:2:1, it was complete within 15 h at room temperature resulting in a single regioisomer **2a**,[13] which was isolated after workup and crystallization from methanol in an excellent (95%) yield.

In this way, a variety of other glycosyl azides **1** were converted to the corresponding methyl 5-methoxycarbonylmethyl-1-(D-glycosyl)-1,2,3-triazole-4-carboxylates **2**, usually in more than 80% yield after purification (see step a in Scheme 2 and Table 1). Reactions, which were too slow at room temperature, were realized successfully at 45 °C. Most importantly, all reactions proceeded with complete retention of the original anomeric configuration of the starting glycosyl azides and irrespective of the relative 1,2-configuration.[14] For example, the β-azide **1e** was transformed into a non-crystalline nucleoside **2e** and its 5'-*O*-deacylated derivative **2d**. The coupling constant ($J_{1'2'}$ ~ 0 Hz) of **2e** is indicative of the β-configuration, while the latter compound was identical with products of the cyclocondensation of **1d** with DOG and isopropylidenation of **2b**. However, the α-anomeric azide **1f** was converted into a completely different set of products **2f** and **2g** as determined on the basis of the ^{1}H and ^{13}C NMR spectra as well as the optical rotation values. The structure of **2f**, a crystalline solid with mp 204-206 °C, was unambiguously confirmed by X-ray analysis,[15] while the identity of **2g** was established by the 5'-*O*-deacylation of **2f** in boiling methanolic triethylamine. Similarly, each of the anomeric arabino azides **1u** and **1w** was transformed to a corre-



Structures of glycosyl azides 1 and nucleoside analogues 2-8

sponding triazole arabinoside **2u** or **2w**, respectively, as the only nucleosidic product.

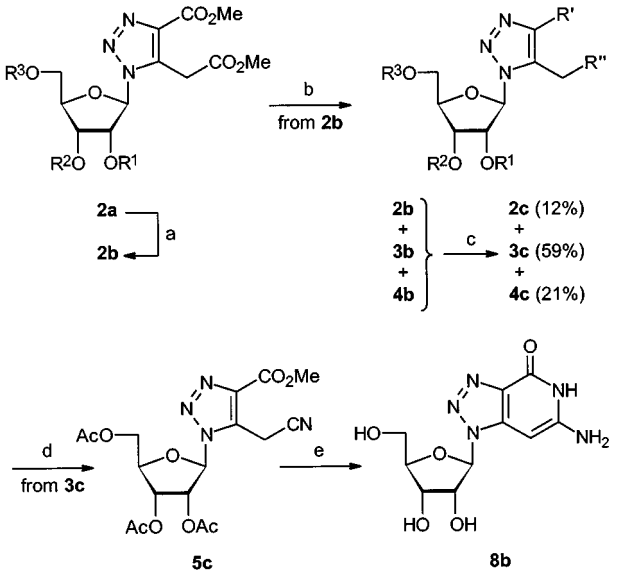
The 1,2,3-triazoles prepared by a Dimroth reaction with DOG were designed to possess suitable functional groups for further processing to the condensed 1,2,3-triazolo[4,5-*c*]pyridine nucleosides. The target 8-aza-3-deazaguanine nucleosides were accessed first by working out the synthesis of the known riboside **8b**. Thus, the protected diester **2a** was first deprotected with NaOMe in methanol to give **2b** (98%), which was subjected to a controlled selective ammonolysis of the aliphatic ester group with methanolic ammonia[16] at 0 °C. The reaction was stopped after 4.5-5 h at ~85% conversion, when the maximum yield (~65%) of the monoamide **3b** was achieved as estimated by HPLC analysis. Isolation and separation of the desired intermediate was aided by the prior acetylation[17] of the crude mixture of *O*-deprotected ammonolysis products. The monoamide **3c** (59%) was then dehydrated[18] with trifluoroacetic anhydride in the presence of pyridine at 5 °C

Table1. Cyclocondensation of glycosyl azides with dimethyl 3-oxoglutarate[a]

azide	product(s)	temp. (°C)	time (h)	yield[b] (%)	$[\alpha]_D^{25}$ (*c*)[c]
1a	**2a**	23	15	95	-27.5 (4.0)
1b	**2b**	23	360	45	-75 (1.0)
1d	**2d**	45	48	82	-68 (4.0)
1e	**2e**	45	24	80	-79 (4.0)
	2d			6	-67 (1.0)
1f	**2f**	45	72	60	-46 (2.0)
	2g			14	-31 (2.0)
1h	**2h**	23	24	93	-2.15 (4.0)
1k	**2k**	45	38	93	-73 (4.0)
1n	**2n**	45	40	88	-67 (4.0)
1r	**2r**	23	40	88	-32 (4.0)
1u	**2u**	45	72	82	-30 (4.0)
1w	**2w**	45	24	80	+78 (4.0)

[a] For a typical procedure see Note 13. [b] Of isolated product, purified by chromatography or crystallization. [c] Measured in $CHCl_3$ except for **2b** (methanol).

to furnish the cyanoester **5c** (86%). Ring closure with simultaneous deprotection by heating with liquid ammonia at 100 °C yielded the target 8-aza-3-deazaguanosine (**8b**) in 77% yield after purification by chromatography as a brownish yellow foam (Scheme 1).

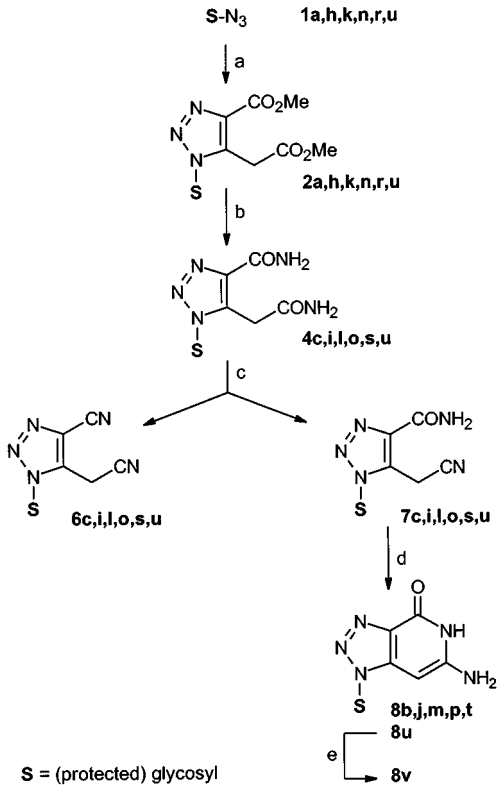


Scheme 1. (a) NaOMe, MeOH, 23 °C, 2 h; (b) NH_3, MeOH, 0 °C, 4.5-5 h; (c) Ac_2O (3.6 eq.), Et_3N (4 eq.), cat. DMAP, MeCN, 23 °C, 1 h; (d) $(CF_3CO)_2O$ (1 eq.), pyridine (2 eq.), THF, 5 °C, 8 min, then warming to 23 °C; (e) NH_3 liq., 100 °C, 17 h.

An alternative approach involved the complete ammonolysis of the deblocked diester **2b** by methanolic ammonia for 1 d at room temperature and subsequent acetylation to give the diamide **4c** (91%). This was selectively dehydrated by a limited amount (1.3 eq.) of trifluo-

roacetic anhydride in the presence of pyridine (2.6 eq.) in THF at -12 to -2 °C, predominately at the aliphatic carboxamide group to furnish the cyanoamide **7c** (65%) along with a small amount of the dinitrile **6c**, which did not interfere with the isolation of **7c**. It is interesting to note, that neither the controlled ammonolysis of the diester **2b** nor dehydration of the diamide **4c** were chemospecific for the aliphatic carboxylic ester derivative when compared to the corresponding reactions of other azoles, containing less than three *N*-atoms within the ring.[19] This effect can be attributed to the increased electron-withdrawing ability of the triazole ring, increasing the reactivity of the aromatic carboxylic acid derivative relative to the aliphatic one. Final cyclization of **7c** and concomitant deprotection with 1 M triethylamine in aq. methanol afforded the crude 8-aza-3-deazaguanosine[20] (**8b**, 72%) as an analytically pure ivory colored powder. The overall yield of **8b** from **1a** via the cyanoamide ring closure[21] was slightly higher (42%) *vs*. that of the cyanoester method (38%), yet, more importantly, provided the pure target nucleoside, free of highly colored impurities. For this very advantage, the cyanoamide method was adopted for the synthesis of other 8-aza-3-deazaguanine nucleosides without further optimization (Scheme 2, Table 2).

Thus, starting from β-D-glycosyl azides **1h**,**k**,**n**,**r**,**u** the first four steps: Dimroth reaction with DOG, deacylation, ammonolysis and acetylation were carried out without purification of intermediates, except for the unprotected diamide **4m**, which crystallized with ease. Pure per-*O*-acetylated diamides **4** were obtained after chromatography or crystallization in 50-57% overall yields. The arabino-diamide **4u** with *O*-benzyl protecting groups was prepared similarly in 56% overall yield from **1u** without the need for deprotection and reprotection steps. Selective dehydration of the *O*-protected diamides **4** was performed in THF as described for the ribo derivative **4c** above, except for **4s**, where DMF was used instead due to its low solubility in THF. Cyanoamides **7** were isolated as major products (44-83%) along with dinitriles **6** (5-10%) by chromatography on silica gel. Syntheses of 8-aza-3-deazaguanine nucleosides **8** were accomplished by ring closure of cyanoamides **7** in basic medium. Per-*O*-acetates were simultaneously deprotected, while 8-aza-3-deazaguanine arabinoside **8v** was obtained after hydrogenolytic debenzylation[22] of **8u** with cyclohexene in the presence of



Scheme 2 (a) dimethyl 3-oxoglutarate (2 eq.), K_2CO_3 (1 eq.), DMSO, conditions as in Table 1; (b) i: NaOMe, MeOH, 23 °C, 2-16 h; ii: NH_3, MeOH, 23 °C, 1 d; iii: Ac_2O, Et_3N, cat. DMAP, MeCN, 23 °C, 1-3 h (for **2u** only step ii necessary); (c) $(CF_3CO)_2O$ (1.3 eq.), pyridine (2.6 eq.), THF (DMF for **4s**), -12 to -2 °C, 35-60 min, then warming to 23 °C; (d) 1 M Et_3N in 80% aq. MeOH, 23 °C, up to 6 d and/or reflux, 6.5-24 h, (e) cyclohexene, EtOH, 20% $Pd(OH)_2$/C, reflux, 45 h.

20% $Pd(OH)_2$ on carbon. The β-configuration of compounds **8b**,**j**,**m**,**p**,**t**,**v** and, consequently, all intermediates derived from the starting β-D-glycosyl azides was determined by the ^{1}H NOE difference NMR spectroscopy. The key NOE enhancements were between H-7 and H-3' and H-2' on the β-side and between H-1' and H-4' on the α-side of the sugar moieties. In addition, the C(1')-F coupling constants in ^{13}C NMR spectra of 2'-deoxy-2'-fluoro-β-D-arabinofuranosyl compounds **1r**, **2r**, **4s**, **6s**, **7s**, and **8t**

Table 2. Synthesis of 8-aza-3-deazaguanine nucleosides **8** *via* the ring closure of cyanoamides **7**.

		yield (%)			
glycosyl	**1**	**4**[a]	**6**	**7**	**8**
β-D-ribofuranosyl	**1a**	**4c** (89)	**6c** (-)	**7c** (65)	**8b** (72)
β-D-xylofuranosyl	**1h**	**4i** (56)	**6i** (7)	**7i** (68)	**8j** (57.5)
3'-deoxy-β-D-*erythro*pentofuranosyl	**1k**	**4l** (57)	**6l** (5)	**7l** (83)	**8m** (79)
2'-deoxy-β-D-*erythro*pentofuranosyl	**1n**	**4o** (50.5)	**6o** (8)	**7o** (76)	**8p** (68)
2'-deoxy-2'-fluoro-β-D-arabinofuranosyl	**1r**	**4s** (52.5)	**6s** (10)	**7s** (44)	**8t** (73)
β-D-arabinofuranosyl	**1u**	**4u** (56)	**6u** (9.6)	**7u** (81.5)	**8u** (90.5) → **8v** (74)

[a] Overall yield from **1**.

($^2J_{C(1'),F}$ = 17.1 ± 0.0 Hz) was found to be highly diagnostic for the β-configuration.[23]

In conclusion, we have developed an efficient method for the stereospecific formation of single *N*-1(3)-glycosylated 1,2,3-triazole regioisomers, convertible to a variety of 8-aza-3-deazapurine nucleosides. In this work, an efficient route for the preparation of 8-aza-3-deazaguanine nucleosides was demonstrated, however, by a proper choice of synthetic methods, derivatives with diverse substitution pattern (8-aza-3-deazaadenines, -xanthines, -hypoxanthines, etc.) should be accessible. The dinitrile **6c**, for example, which was more conveniently prepared by dehydration of both carboxamide groups of **4c**, was found to be a useful precursor to 8-aza-3-deazaisoguanosine.[24]

Acknowledgement

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(13) Typical experimental procedure for the Dimroth reaction of **1a** with DOG: To a solution of **1a** (24.40 g, 50 mmol) and DOG (17.4 g, 100 mmol) in DMSO (60 mL) was added dried and finely ground K_2CO_3 (6.9 g, 50 mmol). The heterogeneous mixture was stirred at room temperature for 15 h and poured into an ice-water mixture (0.5 L). The solid was filtered and washed with water (1 L). The filter cake was dissolved in ethyl acetate (300 mL), the organic phase was washed with 1 M Na_2CO_3 (2 x 200 mL), 0.1 M HCl (200 mL) and brine (200 mL) and dried (Na_2SO_4). Concentration afforded almost colorless foam (32.6 g), which was crystallized from methanol to give **2a** (30.48 g, 95%) as very small needles with mp 110-113 °C; ^{1}H NMR(300 MHz, $CDCl_3$): δ 3.69, 3.94 (2 s, 6, 2 CH_3), 4.18, 4.39 (2d, 2, CH_2; J_{gem} 17.1 Hz), 4.51 (dd, 1, H-5'a; $J_{5'a,5'b}$ 12.2, $J_{4',5'a}$ 4.6 Hz), 4.80 (dd, 1, H-5'b; $J_{4',5'b}$ 3.5 Hz), 4.90 (ddd, 1, H-4'), 6.24 (dd, 1, H-3'; $J_{2',3'}$ 5.1, $J_{3',4'}$ 7.1 Hz), 6.36 (d, 1, H-1'; $J_{1',2'}$ 1.95 Hz), 6.58 (dd, 1, H-2'), 7.34-7.63 and 7.92-8.05 (2m, 15, Ar-H). ^{13}C NMR(75.4 MHz, $CDCl_3$): δ 28.7 (CH_2), 52.0, 52.8 (2 CH_3), 63.0 (C-5'), 71.4 (C-3'), 74.9 (C-2'), 81.3 (C-4'), 89.1 (C-1'), 128.3-133.8 (Ph-C), 135.8, 137.5 (C-4, 5), 161.3, 164.9, 165.0, 165.9, 167.7 (5 CO). IR (film):1732 (C=O), 1268 (benzoate C-O), 1124 (PhCOO-C), 712 cm^{-1} (benzoate). MS (EI): m/z 643 (M^+), 445 ($[M-B]^+$, 9%), 105 (100). Anal. calcd for $C_{33}H_{29}N_3O_{11}$ (643.61): C, 61.58; H, 4.54; N, 6.53. Found: C, 61.53; H, 4.54; N, 6.50.
(14) The stereochemistry of the Dimroth reaction of glycosyl azides with DOG is in sharp contrast to that observed with cyanoacetamide, which was reported to yield 1,2-*trans* nucleosides exclusively or predominately from either 1,2-*trans* or 1,2-*cis* glycosyl azides: Tolman, R. L.; Smith, C. W.; Robins, R. K. *J. Am. Chem. Soc*. **1972**, *94*, 2530; Smith, C. W.; Sidwell, R. W.; Robins, R. K.; Tolman, R. L. *J. Med. Chem*. **1972**, *15*, 883; Chretien, F.; Gross, B. *Tetrahedron* **1982**, *38*, 103. This difference may be attributed to much more favourable intramolecular triazene *N*-atom to carbonyl group cyclization in the glycosyl azide-DOG adduct as opposed to the cyclization to cyano group in the glycosyl azide-cyanoacetamide adduct. For this reason, the competitive anomerization process in the former case should be effectively supressed.
(15) All new compounds were characterized by spectroscopic (NMR, IR, and MS) and analytical methods (microanalysis and/or HRMS) including an X-ray analysis of compound **2f**. Details will be provided in a full paper.
(16) Ammonia, saturated in methanol at 0 °C, was used.
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(20) **8b**: mp 245 °C (dec.), $[\alpha]_D^{25}$ -117 (*c* 1.00, DMSO), {lit.[8] mp 239-241 °C (dec.), $[\alpha]_D^{25}$ -123.2}; ^{1}H NMR(300 MHz, DMS*O*-d_6): δ 3.42-3.62 (m, 2, H-5'a,5'b), 3.97 (ddd, 1, H-4'), 4.19 (ddd, 1, H-3'), 4.63 (ddd, 1, H-2'), 4.86 (t, 1, OH; J 5.4 Hz), 5.27 (d, 1, OH; J 5.2 Hz), 5.49 (s, 1, H-7), 5.55 (d, 1, OH; J 5.9 Hz), 5.82 (d, 1, H-1'; $J_{1',2'}$ 5.1 Hz), 6.08 (br s, 2, NH_2), 10.71 (br s, 1, NH). ^{13}C NMR(75.4 MHz, DMS*O*-d_6): d 62.34

(C-5'), 68.31 (C-7), 71.03 (C-3'), 73.44 (C-2'), 86.06 (C-4'), 90.27 (C-1'), 130.15 (C-3a), 143.30 (C-7a), 150.98 (C-6), 156.36 (C-4). IR (KBr):3376, 3343, 3186, 1685, 1622, 1590, 1388, 1124, 1106, 1047 cm^{-1}. ^{1}H-, ^{13}C NMR, and IR data were in complete agreement with the reported values.[7,8] MS (FAB): m/z 284 $(MH)^+$. UV (pH 11): λ_{max} 218, 286 nm. Anal. calcd for $C_{10}H_{13}N_5O_5$ (283.25): C, 42.41; H, 4.63; N, 24.73. Found: C, 42.15; H, 4.64; N, 24.71.

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