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N-Oxides of Adenosine-Type Nucleosides Undergo Pyrimidine Ring Opening and Closure To Give 5-Amino-4-(1,2,4-oxadiazol-3-yl)imidazole Derivatives†

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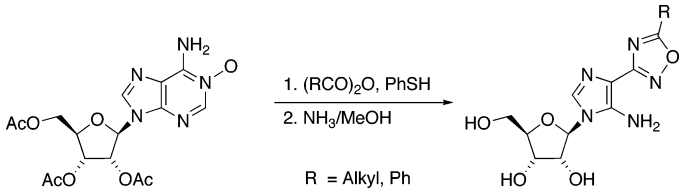
ABSTRACT



Treatment of acylated adenosine *N*-oxides with carboxylic anhydrides and thiophenol resulted in pyrimidine ring opening followed by exocyclic ring closure. Ammonolysis gave 5-amino-4-(5-substituted-1,2,4-oxadiazol-3-yl)-1-(β-D-ribofuranosyl)imidazole derivatives, whereas iodine in methanol selectively unmasked the 5-amino group. Related flexible nucleoside analogues can be prepared from adenine-type precursors.

Separation of the fused imidazole and pyrimidine rings of purine nucleosides increases conformational flexibility, and such shape-modified analogues have been synthesized to investigate triple helix formation[1] and as probes for the study of enzyme interactions.[2] Binding sites on enzymes and other proteins have varying degrees of freedom, and the inherently greater flexibility of ring-linked nucleoside analogues[2] might result in enhanced monomer−protein affinity in favorable cases. Syntheses of such "fleximers" have employed cross-coupling reactions and multistep linear approaches.

We attempted to apply chemistry that has been used with pyridine and quinoline *N*-oxides[3] to convert adenosine *N*-oxides into 2-(substituted)adenosines. However, a product resulting from pyrimidine ring opening and exocyclic ring closure was isolated upon treatment of an adenosine *N*-oxide with acetic anhydride in pyridine. It is known that *N*-oxides of purines and pyrimidines undergo ring opening and rearrangement reactions, many of which have been studied with stable heterocyclic bases.[4] We now report mild conditions with nucleoside derivatives that provide ready access to new "flexible" ring-linked nucleoside analogues.

Brown and co-workers[5] had noted that a number of intermediates were formed upon treatment of adenine 1-oxide (**1**) with acetic anhydride under different reaction conditions (Scheme 1). The imine enol acetate **3a** was postulated to result from attack of acetate at C2 of intermediate **2**. Heterolytic fission of the C2−N1 bond and closure of the oxadiazole ring produced **3a**. In situ hydrolysis of **3a** gave

† Nucleic Acid Related Compounds. 138. Paper 137: Zhong, M.; Nowak, I.; Robins, M. J. *J. Org. Chem.*, **2006**, *71*, 7773−7779.

(1) (a) Wang, W.; Purwanto, M. G. M.; Weisz, K. *Org. Biomol. Chem.* **2004**, *2*, 1194−1198. (b) Lengeler, D.; Weisz, K. *Nucleosides Nucleotides* **1999**, *18*, 1657−1658.

(2) (a) Seley, K. L.; Zhang, L.; Hagos, A. *Org. Lett.* **2001**, *3*, 3209−3210. (b) Seley, K. L.; Zhang, L.; Hagos, A.; Quirk, S. *J. Org. Chem.* **2002**, *67*, 3365−3373. (c) Seley, K. L.; Salim, S.; Zhang, L. *Org. Lett.* **2005**, *7*, 63−66. (d) Seley, K. L.; Salim, S.; Zhang, L.; O'Daniel, P. I. *J. Org. Chem.* **2005**, *70*, 1612−1619.

(3) Manley, P. J.; Bilodeau, M. T. *Org. Lett.* **2002**, *4*, 3127−3129.

(4) Brown, G. B. *Prog. Nucleic Acid Res.* **1968**, *8*, 209−255.

(5) Stevens, M. A.; Smith, H. W.; Brown, G. B. *J. Am. Chem. Soc.* **1960**, *82*, 1148−1152.

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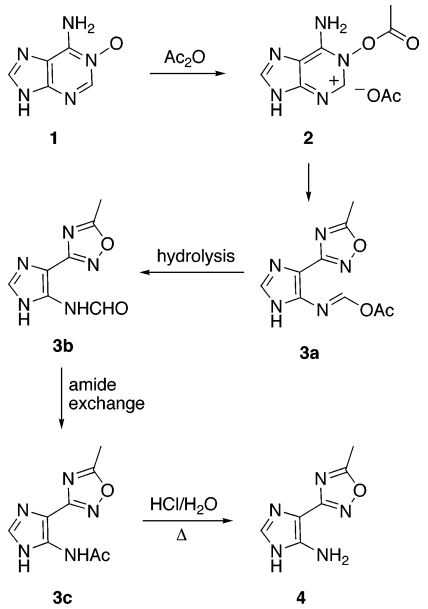
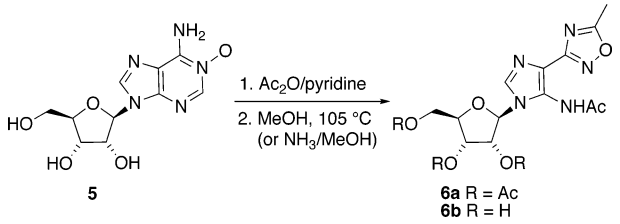
Scheme 1. Ring Opening/Closure of Adenine *N*-Oxide in Ac_2O



formamido derivative **3b**, which underwent amide exchange to give acetamido derivative **3c**. The resulting mixture of **3b** and **3c** was converted into **4** by treatment with hydrochloric acid at reflux.

We subjected *N*-oxide **5** to Ac_2O/pyridine (Scheme 2). The

Scheme 2. Ring Opening/Closure of Adenosine *N*-Oxide in Ac_2O/Pyridine

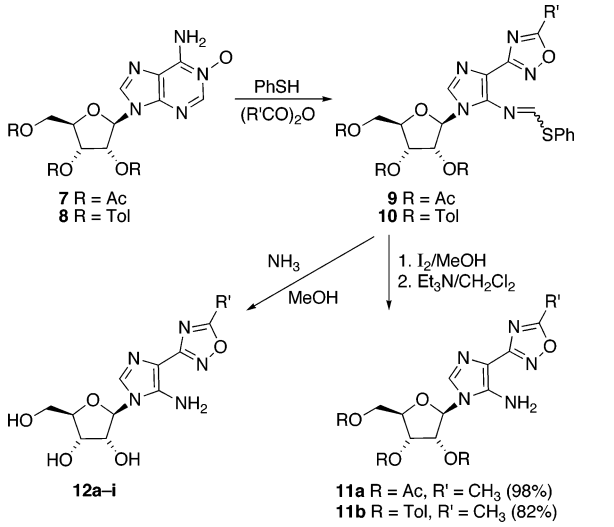


dark mixture contained two closely migrating (TLC) products, and treatment of the mixture with superheated MeOH[6] gave a major product consistent with structure **6a**. Treatment of the mixture with NH_3/MeOH at ambient temperature also cleaved the *O*-acetyl groups to give **6b**. Prolonged heating at 80 °C produced an additional UV-absorbing compound with similar TLC mobility.

Our recent methodology[6] was used for the preparation of 2′,3′,5′-tri-*O*-acyladenosine derivatives. Selection of appropriate acyl groups gave organic-soluble *N*-oxides and readily crystallized derivatives. Oxidation[7] of 2′,3′,5′-tri-*O*-acetyladenosine[6] gave the protected adenosine *N*-oxide **7** (Scheme 3) whose nonpolar solubility circumvented the need

(6) Nowak, I.; Conda-Sheridan, M.; Robins, M. J. *J. Org. Chem.* **2005**, *70*, 7455−7458.

Scheme 3. Ring Opening/Closure of Adenosine *N*-Oxides with Acid Anhydrides and Thiophenol



for pyridine as solvent. Addition of thiophenol (a softer and stronger nucleophile than acetate) also permitted milder conditions.[8] An exothermic reaction (**7**/PhSH/Ac_2O) occurred to give **9a** (R′ = Me) (*E* and *Z* isomers, ∼8:1). The ^{1}H NMR spectrum of the major isomer of **9a** had a signal at δ 9.8 ppm (CH=N) and also showed the presence of a phenylsulfanyl group. Treatment with NH_3/MeOH at 50 °C removed the *O*-acetyl protecting groups as well as the phenylsulfanylmethylene moiety to give crystalline **12a** (R′ = CH_3). It is noteworthy that similar treatment of **9a** with aqueous ammonia gave mixtures of poorly differentiated products that might result from partial hydrolysis of the 1,2,4-oxadiazole ring. Brief exposure of **9a** to I_2 (0.5 mol equiv) in hot MeOH[9] caused selective deprotection of the amino group at C5. Chromatography separated the yellow hydroiodide salt of **11a**. Evaporation of volatiles followed by neutralization (Et_3N/CH_2Cl_2) and chromatography gave the free amine. TLC spots of the UV-sensitive **11a**, **11b**, and **12a** developed deep purple colors. The structures of **11b** and **12a** were confirmed by X-ray crystallography.

Anhydrides derived from aliphatic acids reacted rapidly with **7** in the presence of excess thiophenol. Deprotected products **12a**−**i** (Table 1) were obtained by ammonolysis of intermediates **9a**−**i**. Increases in the steric bulk of the alkyl groups adjacent to the anhydride carbonyls had little effect on reaction rates or yields (entries 1−5). The longer-chain aliphatic and benzoic anhydrides required a solvent (1,2-dichloroethane) and gave lower yields (entries 6−9). Bz_2O in excess (6 equiv) and longer reaction times (1−2 h) were required for conversion of **7** into **9i**.

(7) (a) Kikugawa, K.; Suehiro, H.; Yanase, R.; Aoki, A. *Chem. Pharm. Bull.* **1977**, *25*, 1959−1969. (b) Kwong, C. D.; Krauth, C. A.; Shortnacy-Fowler, A.; Arnett, G.; Hollingshead, M. G.; Shannon, W. M.; Montgomery, J. A.; Secrist, J. A., III. *Nucleosides Nucleotides* **1998**, *17*, 1409−1443.

(8) Other additions [e.g., TMS−N_3/Ac_2O, TMS−Cl/Ac_2O, CH_3NO_2/Ac_2O, PCl_3/Ac_2O, $SOCl_2$/Ac_2O, and $BnN(Et)_3Cl$/Ac_2O] were ineffective, and addition of phenol or methanol gave lower yields of related intermediates.

(9) Szarek, W. A.; Zamojski, K. N.; Tiwari, K. N.; Ison, E. R. *Tetrahedron Lett.* **1986**, *27*, 3827−3830.

Table 1. Conversion[a] of *N*-Oxide **7** into **9** and **12**

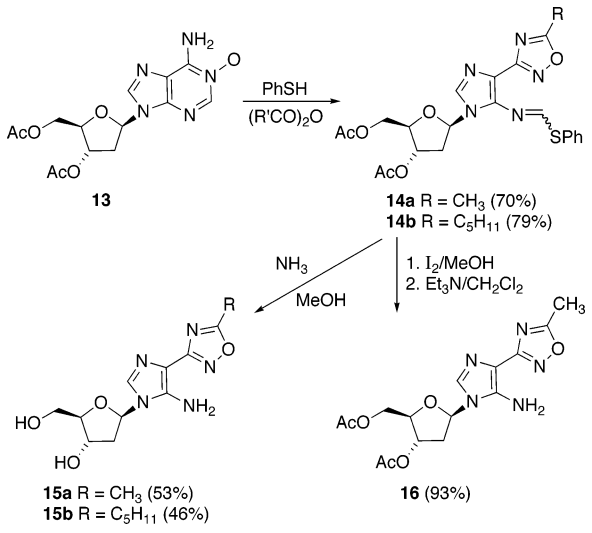
entry	R′	yield (%)[b]	
1	CH_3	**9a** (78)	**12a** (59)
2	C_2H_5	**9b** (82)	**12b** (63)
3	C_3H_7	**9c** (68)	**12c** (49)
4	$CH(CH_3)_2$	**9d** (83)	**12d** (47)
5	$C(CH_3)_3$	**9e** (60)	**12e** (46)
6	C_5H_{11}	**9f** (45)	**12f** (29)
7	C_7H_{15}	**9g** (43)	**12g** (32)
8	C_9H_{19}	**9h** (40)	**12h** (28)
9	Ph	**9i** (51)	**12i** (41)

[a] The general procedures were used (Supporting Information). [b] Isolated yields beginning with **7** (one step for **9**, two steps for **12**).

Immediate evolution of gas occurred upon addition of acetic formic anhydride to **7**, and a complex mixture was formed. Such a mixture also resulted from treatment of **7** with the anhydrides of trifluoroacetic or chloroacetic acid. Recovery of starting materials after prolonged reflux of a solution of the *N*-oxide **7** and phenyl thiobenzoate in 1,2-dichloroethane indicated that transesterification of the *N*-oxide **7** by the thioester did not occur.

It is noteworthy that the less-stable 2′-deoxy *N*-oxide **13** readily underwent conversions to intermediates **14a** (70%) and **14b** (79%) [as well as two-step conversions via ammonolysis to **15a** (53%) and **15b** (46%)] (Scheme 4).

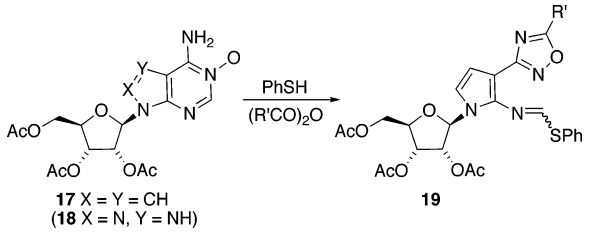
Scheme 4. Ring Opening/Closure of 2′-Deoxyadenosine *N*-Oxide



Treatment of intermediate **14a** with I_2/MeOH gave **16** (93% from **14a**, 65% from **13**).

The acetylated tubercidin *N*-oxide **17** (Scheme 5) and 2′,3′,5′-tri-*O*-acetylformycin *N*-oxide (**18**) were subjected to our standard conditions. The expected intermediate **19** was obtained from **17** in low yield (24%), but ammonolysis of **19** (NH_3/MeOH) gave an unstable, deeply colored mixture,

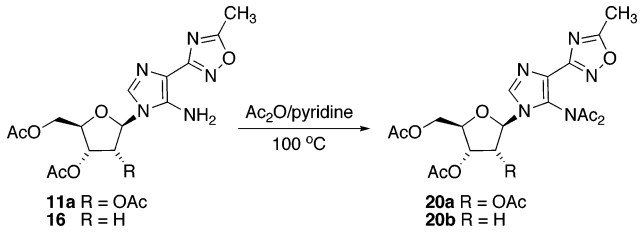
Scheme 5. Ring Opening/Closure of Related *N*-Oxides



which is typical with aminopyrrole derivatives.[10] Standard treatment of the protected formycin *N*-oxide **18** gave a complex mixture that was not investigated further.

Treatment of the 5-amino compounds **11a** and **16** with Ac_2O/pyridine for 1 h at 100 °C resulted in formation of the 5-(*N*,*N*-diacetyl) derivatives **20a** and **20b**, respectively (Scheme 6). It is noteworthy that **11a** was unchanged by

Scheme 6. Acetylation of **11a** and **16**



such treatment at ambient temperature (and ∼10% of **11a** was detected even at 90 °C). Thus, acetylation of the amino group did not occur under conditions that usually produce amides, and diacetylation resulted under more forcing conditions. Steric hindrance and/or delocalization of the lone-pair electrons into the heteroaromatic ring might seriously retard the rate of amine acetylation.

We have reported the structures and syntheses of several 6-(heteroaryl)purine nucleosides in which the heteroaryl and

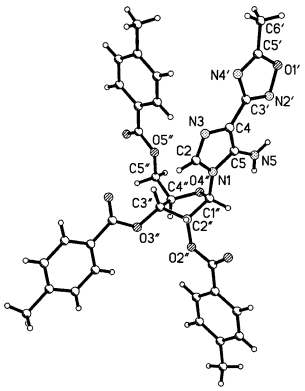


Figure 1. X-ray crystal structure of **11b**.

purine rings approach coplanarity in the solid state.[11] Favorable $\pi-\pi$ interactions contribute to lower energies in coplanar conformations.[12] Our X-ray crystal structures of protected **11b** (Figure 1) and deprotected **12a** (Figure 2) show

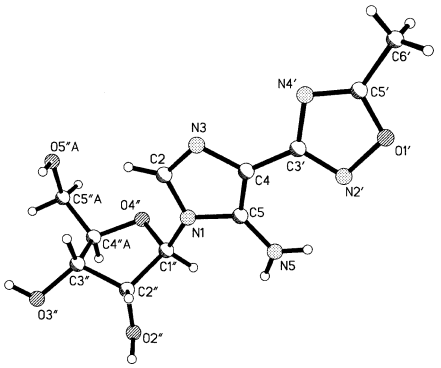


Figure 2. X-ray crystal structure of **12a**.

the 1,2,4-oxadiazole and imidazole rings approaching coplanarity (~8° projection angle for the rings of **11b**; ~11° for **12a**). Steric and/or conjugative electron donation effects might retard nucleophilic attack by the 5-amino group at the electrophilic carbonyl groups of carboxylic anhydrides. Elevated temperatures would change rotamer populations, which might make amine acetylation more favorable. The 5-acetamido group would be a weaker electron donor into the imidazole ring but could undergo acetylation at 100 °C. Treatment of the 2′-deoxy-5-(*N*,*N*-diacetyl) compound **20b** with NH_3/MeOH at 50 °C resulted in removal of one *N*-acetyl group and cleavage of the glycosyl bond to give **3c**. Our X-ray crystal structure of **3c** revealed that its rings are nearly coplanar (projection angle of ~5°), but the two rings are inverted relative to the conformations of **11b** and **12a** (Supporting Information).

In conclusion, our treatment of *N*-oxides of hydroxyl-protected adenosine, 2′-deoxyadenosine, and tubercidin (7-deazaadenosine) with carboxylic acid anhydrides in the presence of thiophenol produced 4-(5-substituted-1,2,4-oxadiazol-3-yl) nucleoside analogues. Deprotection of the 5-amino group was effected selectively with iodine in hot methanol, and complete deblocking occurred in methanolic ammonia at 50 °C. Acylation of the 5-amino group did not occur at ambient temperature, and 5-(*N*,*N*-diacetyl) derivatives were produced at 100 °C. Orientations of the linked heterocyclic rings approached coplanarity (in the solid state), which indicates possible constraints of conformational flexibility. However, hydrogen bonding of protein amino acid residues with acceptors and donors in the fleximer analogues might outweigh such stereoelectronic effects. Evaluations of biological response properties are underway.

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Supporting Information Available: Experimental procedures, data, NMR spectra, and X-ray crystal structures with CIF data for **3c**, **11b**, and **12a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Zhong, M.; Nowak, I.; Cannon, J. F.; Robins, M. J. *J. Org. Chem.* **2006**, *71*, 4216−4221.

(12) Carra, C.; Bally, T.; Albini, A. *J. Am. Chem. Soc.* **2005**, *127*, 5552−5562.