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1,3-DIPOLAR CYCLOADDITION REACTIONS OF NITRILE OXIDES WITH 2',3'-DIDEHYDRO-2',3'-DIDEOXYTHYMIDINE (d4T)

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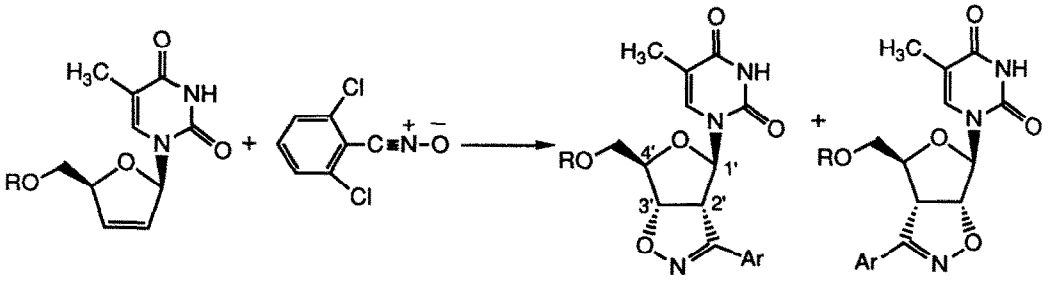
Summary: 1,3-Dipolar cycloaddition reactions of 2,6-dichlorobenzonitrile oxide (**2**) with the unsaturated furanose moiety of 2',3'-didehydro-2',3'-dideoxythymidine derivatives (**1a** and **1b**) are described.

A number of nucleosides with modified sugar moieties are currently undergoing evaluation as antiviral agents,[1] and modifications at the 2'- or 3'-position of the furanose have been extensively studied.[2] However, to our knowledge, no report exists about cycloadditions of nitrile oxide to the unsaturated sugar of nucleosides.

In our continuing research program on cycloaddition reactions of nitrile oxides with pyrimidine nucleosides,[3] we examined reactions of 2',3'-didehydro-2',3'-dideoxythymidine (d4T, **1a**)[4] and its derivative **1b** with 2,6-dichlorobenzonitrile oxide (**2**).[5]



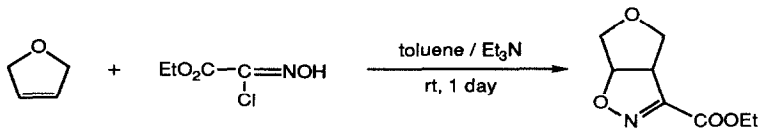
1 **2** **3** **4**

a: R = H 67% (3 : 2)
b: R = $SiMe_2$t-Bu 96% (3 : 1)

The reaction of **2** (generated *in situ* from 2,6-dichlorobenzohydroximoyl chloride by treatment of triethylamine) with d4T (**1a**) in DMF at room temperature for 3 days afforded a mixture of regioisomeric cycloaddition products **3a** and **4a** in 67% isolated yield.[6] The regioisomers could not be separated completely by chromatography. However, we were able to determine the composition ratio **3a** : **4a** (3 : 2) from its ^{1}H NMR spectrum. The peak corresponding to the proton at the 3'-position of **3a** appeared 1 ppm downfield relative to the 3'-proton in **4a** due to the deshielding effect of the oxygen atom in the isoxazoline moiety.[7] Treatment of 5'-*O*-t-butyldimethylsilyl derivative **1b** with isolated 2,6-dichlorobenzonitrile oxide (**2**) in THF-toluene at 70~80 °C for 2 days gave a 3 : 1 regioisomeric mixture of the cycloaddition products **3b** and **4b** in 96% isolated yield.[8] The major isomer was isolated by flash chromatography (SiO_2, CH_2Cl_2/ acetone, 20 : 1), and its regiochemistry determined as 3b. The steric repulsion between the t-butyldimethylsilyoxy methylene group and the 2,6-dichlorophenyl group in the incoming nitrile oxide might affect preferential formation of **3b** over **4b**. The cycloadditions of the nitrile oxide apparently proceed *anti* to the sterically hindered 1',4'-substituents on the basis of the work of Caramella et al.[9] In all cases we were not able to detect any *syn*-adducts.

Attempted reactions of the less stable carbethoxyformonitrile oxide with d4T derivatives were unsuc-

cessful and furnished none of the desired cycloaddition products. The reaction of carbethoxyformonitrile oxide with unsubstituted 2,5-dihydrofuran (**5**) gave the corresponding cycloaddition product **6** in 55% isolated yield.[10]



5 **6**

From these results, the failure of the reaction of carbethoxyformonitrile oxide with d4T derivatives might be attributed partly to the steric repulsion by the 1',4'-substituents and the unfavorable puckering effect of the dihydrofuranose moieties.

Further studies with other nucleosides and evaluation of biological activities of the products are in progress.

References and Notes

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3. Reactions of nitrile oxides with the 5,6-double bond of pyrimidine nucleosides have been carried out, and will be published elsewhere.
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5. J. N. Kim and E. K. Ryu, *Synth. Commun.*, **20**, 1373 (1990).
6. Characterization of **3a**: ^{1}H NMR (300 MHz, acetone-d_6) δ 1.76 (d, J=1.2 Hz, 3H), 3.90-4.10 (m, 2H, H5', H5"), 4.25 (m, 1H, H4'), 4.60 (t, 1H, OH, D_2O exchangeable), 4.76 (dd, J=2.4 and 9.8 Hz, 1H, H2'), 5.65 (dd, J=5.2 and 9.8 Hz, 1H, H3'), 6.19 (d, J=2.4 Hz, 1H, H1'), 7.45-7.67 (m, 3H, aromatic), 7.70 (d, J=1.2 Hz, 1H, H-6), 9.98 (brs, 1H, NH, D_2O exchangeable). **4a**: ^{1}H NMR (300 MHz, acetone-d_6) δ 1.85 (d, J=1.2 Hz, 3H), 3.26 (t, 1H, OH, D_2O exchangeable), 3.52-3.80 (m, 2H, H5', H5"), 4.45 (m, 1H, H4'), 4.65 (ddd, J=0.5, 3.9, and 9.9 Hz, 1H, H3'), 5.73 (dd, J=3.9 and 9.9 Hz, 1H, H2'), 6.10 (d, J=3.9 Hz, 1H, H1'), 7.45-7.67 (m, 3H, aromatic), 7.78 (d, J=1.2 Hz, 1H, H-6), 10.25 (brs, 1H, NH, D_2O exchangeable); FABMS ($C_{17}H_{15}N_3O_5Cl_2$) 412 (M^++H).
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8. Characterization of **3b**: ^{1}H NMR (300 MHz, acetone-d_6) δ 0.19 and 0.20 (two s, each 3H), 0.99 (s, 9H), 1.85 (d, J=1.2 Hz, 3H), 4.05-4.20 (m, 2H, H5', H5"), 4.32-4.37 (m, 1H, H4'), 4.83 (dd, J=2.6 and 9.9 Hz, 1H, H2'), 5.63 (dd, J=5.0 and 9.9 Hz, 1H, H3'), 6.19 (d, J=2.6 Hz, 1H, H1'), 7.52 (d, J=1.2 Hz, 1H, H-6), 7.40-7.70 (m, 3H, aromatic), 10.0 (brs, 1H, NH); EIMS (20 eV) m/z 468 (M^+-tBu, 30), 342 (57), 268 (76), 201 (100), 183 (80). **4b**: ^{1}H NMR (300 MHz, acetone-d_6) δ 0.01 and 0.03 (two s, each 3H), 0.85 (s, 9H), 1.91 (d, J=1.2 Hz, 3H), 3.72-3.95 (m, 2H, H5', H5"), 4.49 (m, 1H, H4'), 4.68 (dd, J=4.4 and 9.9 Hz, 1H, H3'), 5.82 (dd, J=3.3 and 9.9 Hz, 1H, H2'), 6.12 (d, J=3.3 Hz, 1H, H1'), 7.40-7.67 (m, 4H, H-6 and aromatic), 10.25 (brs, 1H, NH).
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10. Characterization of **6**: ^{1}H NMR (300 MHz, acetone-d_6) δ 1.29 (t, J=7.1 Hz, 3H), 3.63-3.73 (m, 2H), 4.11-4.21 (m, 3H), 4.29 (qd, J=7.1 and 0.9 Hz, 2H), 5.44 (dd, J=3.7 and 9.2 Hz, 1H); EIMS (20 eV) m/z 186 (M^++1, 4), 112 (100).