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THE REACTIONS OF 2,6-DICHLOROBENZONITRILE OXIDE WITH THE 5,6-DOUBLE BOND OF CYTOSINE NUCLEOSIDES

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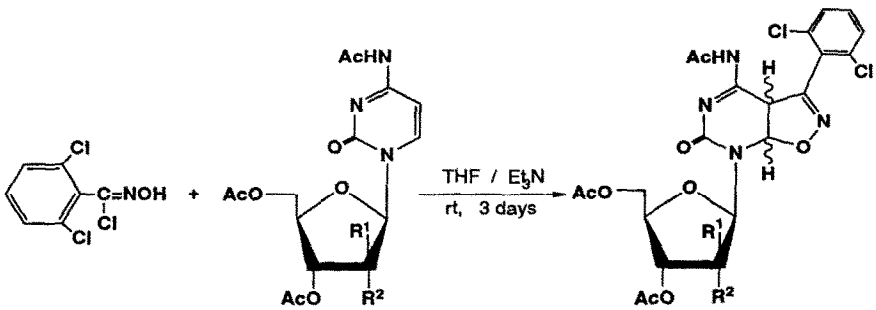
Abstract: The reactions of 2,6-dichlorobenzonitrile oxide with some cytosine nucleosides afforded diastereomeric mixtures of [3+2] cycloaddition products.

Nitrile oxides reacted with various kinds of olefins or acetylenes to afford the synthetically useful isoxazoline or isoxazole derivatives, respectively.[1] Recently, we have reported that the reactions of nitrile oxides with the 5,6-double bond of uracil nucleoside derivatives.[2] The reactions of nitrile oxides with uracil nucleosides afforded the 5-aroylpyrimidine nucleoside oxime derivatives in good yields. In these reactions we could obtain the oxime derivatives *via* the ring-opening reaction of the initially formed [3+2] cycloaddition products. These results prompted us to investigate the reactions of nitrile oxides with cytosine nucleosides which possess different reactivity compared with uracil nucleosides mainly due to the basic nature of cytosine nucleosides.[3] In fact, cytosine nucleosides gave different products compared with those of uracil nucleosides in the reactions with 2,6-dichlorobenzonitrile oxide, thus we report herein the preliminary results.

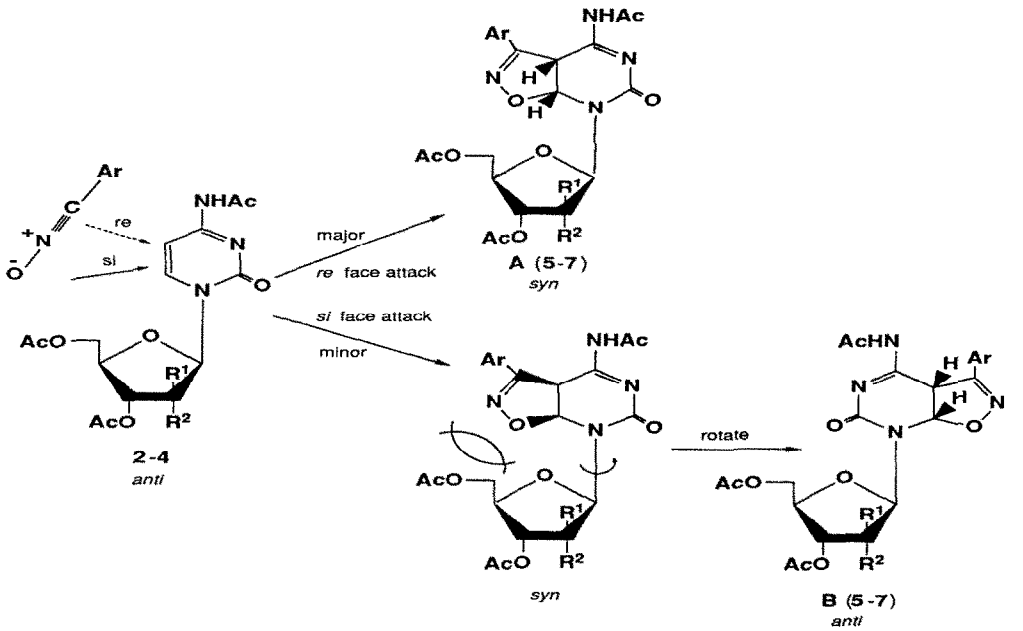
The reactions of 2,6-dichlorobenzonitrile oxide (generated *in situ* from **1**) with acetylated cytosine nucleosides **2-4** afforded the corresponding [3+2] cycloaddition products **5-7** (**Scheme 1**).



1 **2-4** **5-7**

Scheme 1

Thus, the mixture of 2,6-dichlorobenzohydroximoyl chloride (**1**) and *N*-acetyl-2',3',5'-tri-*O*-acetylcytidine (**2**) in tetrahydrofuran was treated with triethylamine (Et_3N) at room temperature, and stirred for 3 days, afforded the cycloaddition product **5**[4] in 62% isolated yield. Similarly **6**[5] and **7**[6] were prepared by the analogous procedure in 88% and 89%, respectively. These cycloaddition products were mixtures of two diastereomers, **A** and **B** (**Scheme 2**).



Scheme 2

The ratios of these diastereomers were determined by ^1H NMR spectra in tetrahydrofuran-d_8, and the results were summarized in **Table I.** The diastereomers were hard to separate in pure state by column chromatography. However, we could separate each diastereomer **5A** and **5B** in somewhat pure state (>95% purity) by Chromatotron (Harrison Research, silica gel 60 FP_{254}, 15% acetone in ether).

Table I. The ratios of diastereomeric mixture 5-7

Starting Material	Product (**A** : **B**)	Yield (%)
2: R^1 = H, R^2 = OAc	**5** (75 : 25)	62
3: R^1 = H, R^2 = H	**6** (89 : 11)	88
4: R^1 = OAc, R^2 = H	**7** (70 : 30)	89

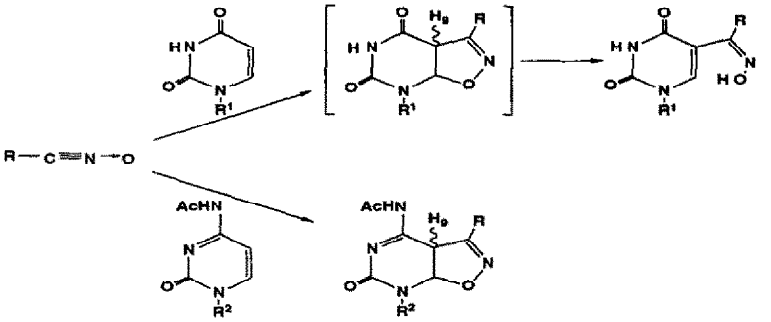
Between the two possible diastereomers, the diastereomer **A** that formed from the *re* face attack of nitrile oxide to the cytosine ring exceeds the other diastereomer **B**. *Si* face attack of nitrile oxide is more difficult by the steric repulsion between the 5'-acetoxy group in sugar moiety and the incoming nitrile oxide. While the *re* face attacked cycloaddition product **A** could remain as *syn* form,[7,8] the *si* face attacked cycloaddition products might rotate about their glycosidic bond to near *anti* form in order to minimize the steric repulsion between the 5'-acetoxy group and the isoxazoline moiety.[8] This assumption was derived from the ^{1}H NMR spectra of the products. The protons at C2' and C3' in **A** shifted upfield due to the anisotropy of the carbonyl group at C6 in **A**.[9] The proton at C1' in **B** shifted upfield due to the same anisotropic effect. The selected ^{1}H NMR data of the products were shown in **Table II.**

Table II. Selected ^{1}H NMR data of diastereomeric mixture of 5-7

Product	H1'	H2'	H3'	H8	H9	NH
5A	6.08	5.27	5.27	6.72	5.49	8.50
5B	5.81	5.38	5.32	6.69	5.51	8.39
6A	6.14	2.28*	5.14*	6.73	5.45	8.53
6B	5.90	2.28*	5.14*	6.69	5.48	8.39
7A	6.24	5.23	4.98	6.83	5.40	8.49
7B	5.89	5.31	5.12	6.73	5.39	8.39

*Peaks were overlapped.

These results were somewhat different with those of uracil nucleosides as shown in **Scheme 3.** For uracil nucleosides, the initially formed [3+2] cycloaddition products were unstable in the reaction conditions, thus we could obtain the ring-opened oxime derivatives as the sole products.[2] These results were derived



Scheme 3

from the different susceptibility of the proton at the C9 position toward base or solvent molecules. The H9 proton in the case of uracil derivatives is acidic due to the adjacent keto group, thus prone to be

attacked by base or solvent. However, for cytosine derivatives the H9 proton is not acidic enough to be ring-opened in the reaction conditions.

The dipolarophilic reactivity of the 5,6-double bond of cytosine nucleosides seemed similar with that of the uracil derivatives. Thus, the reactions of **2** with less stable nitrile oxide such as trifluoroacetonitrile oxide or bromonitrile oxide failed to afford the desired cycloaddition products.

References and Notes

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4. Characterization of **5A**: ^{1}H NMR (300 MHz, THF-d_8) δ 1.78 (s, 3H), 1.98 (s, 3H), 2.06 (s, 3H), 4.15-4.35 (m, 3H, H4', H5', H5"), 5.27 (m, 2H, H2', H3'), 5.49 (d, J = 8.23 Hz, 1H, H9), 6.08 (d, J = 6.97 Hz, 1H, H1'), 6.72 (d, J = 8.23 Hz, 1H, H8), 7.41-7.45 (m, 3H, aromatic), 8.50 (brs, 1H, NH); Anal. Calcd for $C_{24}H_{24}Cl_2N_4O_{10}$: C, 48.08; H, 4.01; N, 9.35. Found: C, 47.92; H, 4.21; N, 9.29. **5B**: ^{1}H NMR (300 MHz, THF-d_8) δ 1.79 (s, 3H), 1.95 (s, 3H), 2.00 (s, 3H), 2.04 (s, 3H), 4.15-4.35 (m, 3H, H4', H5', H5"), 5.32 (m, 1H, H3'), 5.38 (m, 1H, H2'), 5.51 (d, J = 8.18 Hz, 1H, H9), 5.81 (d, J = 6.24 Hz, 1H, H1'), 6.69 (d, J = 8.18 Hz, 1H, H8), 7.41-7.45 (m, 3H, aromatic), 8.39 (brs, 1H, NH).
5. Characterization of **6A**: ^{1}H NMR (300 MHz, THF-d_8) δ 1.79 (s, 3H), 1.99 (s, 3H), 2.02 (s, 3H), 2.28 (m, 2H, H2', H2"), 4.09-4.28 (m, 3H, H4', H5', H5"), 5.14 (m, 1H, H3'), 5.45 (d, J = 8.24 Hz, 1H, H9), 6.14 (t, J = 7.23 Hz, 1H, H1'), 6.73 (d, J = 8.24 Hz, 1H, H8), 7.43 (s, 3H, aromatic), 8.53 (brs, 1H, NH); Anal. Calcd for $C_{22}H_{22}Cl_2N_4O_8$: C, 48.80; H, 4.07; N, 10.35. Found: C, 48.69; H, 4.12; N, 10.12. **6B**: ^{1}H NMR (300 MHz, THF-d_8) δ 1.73 (s, 3H), 1.98 (s, 3H), 2.00 (s, 3H), 2.28 (m, 2H, H2', H2"), 4.09-4.28 (m, 3H, H4', H5', H5"), 5.14 (m, 1H, H3'), 5.48 (d, J = 8.30 Hz, 1H, H9), 5.90 (t, 1H, H1'), 6.69 (d, J = 8.30 Hz, 1H, H8), 7.43 (s, 3H, aromatic), 8.39 (brs, 1H, NH).
6. Characterization of **7A**: ^{1}H NMR (300 MHz, THF-d_8) δ 1.79 (s, 3H), 1.96 (s, 3H), 2.02 (s, 3H), 2.04 (s, 3H), 4.03-4.36 (m, 3H, H4', H5', H5"), 4.98 (m, 1H, H3'), 5.23 (m, 1H, H2'), 5.40 (d, J = 8.26 Hz, 1H, H9), 6.24 (d, J = 4.10 Hz, 1H, H1'), 6.83 (d, J = 8.26 Hz, 1H, H8), 7.41-7.45 (m, 3H, aro matic), 8.49 (brs, 1H, NH); Anal. Calcd for $C_{24}H_{24}Cl_2N_4O_{10}$: C, 48.08; H, 4.01; N, 9.35. Found: C, 48.00; H, 4.27; N, 9.19. **7B**: ^{1}H NMR (300 MHz, THF-d_8) δ 1.79 (s, 3H), 1.99 (s, 3H), 2.01 (s, 3H), 2.03 (s, 3H), 4.03-4.36 (m, 3H, H4', H5', H5"), 5.12 (m, 1H, H3'), 5.31 (m, 1H, H2'), 5.39 (d, J = 8.30 Hz, 1H, H9), 5.89 (d, J = 4.60 Hz, 1H, H1'), 6.73 (d, J = 8.30 Hz, 1H, H8), 7.41-7.45 (m, 3H, aromatic), 8.39 (brs, 1H, NH).
7. The somewhat unfavorable steric hindrance in the *syn* conformer **A** might be released by the C2'-*endo* puckering of the sugar moiety to apart the sugar from the base moiety. See: (a) Davies, D. B.; Danyluk, S. S. *Biochemistry* **1974**, *13*, 4417. (b) Altona, C.; Sundaralingam, M. *J. Am. Chem. Soc.* **1972**, *94*, 8205.
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