Reactivity of Nitrile Oxides toward the 5,6-Double Bond of Uracil Derivatives: Synthesis of Some 5-Aroylpyrimidine Nucleoside Oximes

Jae Nyoung Kim and Eung K. Ryu*

Division of Organic Chemistry, Korea Research Institute of Chemical Technology, Daedeog-Danji, Daejeon 305-606, Korea

Received September 18, 1991

The 5-aroylpyrimidine nucleoside oximes **3-10** were prepared in moderate to good yield by the reaction of the corresponding pyrimidine nucleosides **2a-d** with stable nitrile oxides. The nitrile oxides were generated in situ from the corresponding hydroximoyl chlorides **1a-e**. From these reactions, only the 1,3-addition products **3-10** were obtained. No products of cycloaddition could be isolated. The 1,3-addition products **3-10** could be formed from the ring-opening reaction of the initially formed 1,3-cycloaddition products. Evidence that supports the proposed mechanism came from experiments that used 1,3-dimethyluracil (**13**) as the substrate.

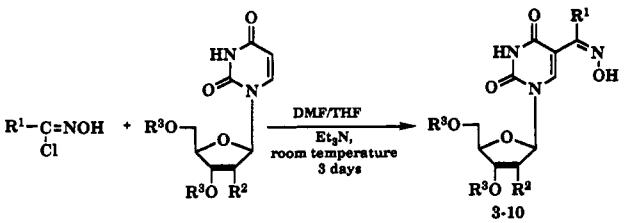
Introduction

The 1,3-dipolar cycloaddition reaction is one of the most powerful tools for the synthesis of heterocyclic compounds.[1] Nitrile oxides are an important class of 1,3-dipoles. The formation of isoxazolines or isoxazoles by the [3 + 2] dipolar cycloaddition of nitrile oxides to olefins or acetylenes has been extensively reviewed.[2] In connection with the reaction of nitrile oxides with olefins or acetylenes, an unusual substitution reaction which gives products of 1,3-addition has also been investigated along with the mechanism of 1,3-dipolar cycloaddition.[3] The reaction of benzonitrile oxide with phenylacetylene is particularly well documented.[3e,f,4] In this instance, the concomitant formation of diphenylisoxazole and an acetylenic oxime was explained in terms of two different pathways: one a concerted cycloaddition and the other a substitution via an electrophilic attack of the nitrile oxide on the triple bond of phenylacetylene. Examples of the formation of oximes by the reaction of nitrile oxides with olefinic dipolarophiles are very rare. For example, the reaction of benzonitrile oxide and furan gave an oxime (1%) in addition to the expected cycloadducts.[5] Only in the reaction of trifluoroacetonitrile oxide with conjugated olefins like styrenes, indenes, and 1,3-dienes were larger amounts of oxime produced.[6] The formation of oximes in these cases was also explained in terms of a two-step substitution via an electrophilic attack of the nitrile oxide.

Although much effort has been devoted to the study of the photodimerization[7] of, and the photocycloadditions[8] to, pyrimidines, there are only a few examples of the use of the 5,6-double bond of pyrimidines as a dipolarophile. The 1,3-dipolar cycloaddition of an azide to pyrimidine rings activated by the presence of a 5-nitro or 5-bromo substituent[9] and the intramolecular cycloadditions of 5'-azido-5'-deoxyuridine derivatives[10] are the only reports of 1,3-dipolar cycloadditions to pyrimidines.

To our knowledge, there were no reports that deal with the reactions of pyrimidines with nitrile oxides. In a continuation of our recent studies of the reactions of nitrile oxides,[11] we examined the cycloadditions of those species

Scheme I



3-10

1a: R^1 = 2,6-$Cl_2C_6H_3$
1b: R^1 = 2-Cl, 6-FC_6H_3
1c: R^1 = 2,6-$F_2C_6H_3$
1d: R^1 = 2,3,5,6-F_4C_6H
1e: R^1 = 2,3,6-$Cl_3C_6H_2$

2a: R^2 = OH, R^3 = H
2b: R^2 = OBz, R^3 = Bz
2c: R^2 = H, R^3 = Ac
2d: R^2 = H, R^3 = H

Table I. Preparation of 5-Aroylpyrimidine Nucleoside Oximes

entry	reactants	product	yield[d] (%)
1	**1a + 2a**	**3**	50
2	**1a + 2b**	**4**	83
3	**1a + 2c**	**5**	65
4	**1a + 2d**	**6**	49
5	**1b + 2d**	**7**	60
6	**1c + 2d**	**8**	71
7	**1d + 2d**	**9**	43
8	**1e + 2d**	**10**	89

[d] Isolated yield. No attempt was made to optimize the yield.

(1) (a) Grundmann, C.; Grünhanger, P. *The Nitrile Oxides*; Springer-Verlag: New York, 1971. (b) Caramella, P.; Grünhanger, P. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984.

(2) (a) Curran, D. P. *Advances in Cycloaddition*; JAI: Greenwich, CN, 1988; p 129. (b) Jäger, V.; Müller, I.; Schohe, R.; Frey, M.; Ehrler, R.; Häfele, B.; Schröter, D. *Lect. Heterocycl. Chem.* **1985**, *8*, 79. (c) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410. (d) Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: New York, 1988. (e) Kanemasa, S.; Tsuge, O. *Heterocycles* **1990**, *30*, 719. (f) Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D. *Synthesis* **1987**, 857.

(3) (a) Baran, J.; Mayr, H. *J. Org. Chem.* **1989**, *54*, 5012. (b) Firestone, R. A. *Tetrahedron* **1977**, *33*, 3009. (c) Huisgen, R. *J. Org. Chem.* **1976**, *41*, 403. (d) Bast, K.; Christl, M.; Huisgen, R.; Mack, W.; Sustmann, R. *Chem. Ber.* **1973**, *106*, 3258. (e) Morrocchi, S.; Ricca, A.; Selva, A.; Zanarotti, A.; Quilico, A. *Rend. Accad. Naz. Lincei.* **1970**, *47*, 231. (f) Morrocchi, S.; Ricca, A.; Zanarotti, A. *Tetrahedron Lett.* **1969**, 3329.

(4) (a) Beltrame, P.; Sartirana, P.; Vintani, C. *J. Chem. Soc. B* **1971**, 814. (b) Battaglia, A.; Dondoni, A.; Mangini, A. *J. Chem. Soc. B* **1971**, 554.

(5) Caramella, P.; Cellerino, G.; Corsico Coda, A.; Gamba Invernizzi, A.; Grünanger, P.; Houk, K. N.; Marinone Albini, F. *J. Org. Chem.* **1976**, *41*, 3349.

(6) Tanaka, K.; Masuda, H.; Mitsuhashi, K. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2061.

(7) (a) *Organic Chemistry of Nucleic Acids*; Kochetkov, N. K., Budovskii, E. I., Eds.; Plenum Press: New York, 1972; Part B, p 543. (b) *Basic Principles in Nucleic Acid Chemistry*; Ts'o, P. O. P., Ed.; Academic Press: New York, 1974; Vol. 1, p 384.

(8) (a) Kaminski, V. V.; Wexler, A. J.; Balchunis, R. J.; Swenton, J. S. *J. Org. Chem.* **1984**, *49*, 2738. (b) Saito, I.; Shimozono, K.; Matsuura, T. *J. Am. Chem. Soc.* **1983**, *105*, 963. (c) Swenton, J. S.; Hyatt, J. A.; Lisy, J. M.; Clardy, J. *J. Am. Chem. Soc.* **1974**, *96*, 4885. (d) Hyatt, J. A.; Swenton, J. S. *J. Am. Chem. Soc.* **1972**, *94*, 7605.

(9) (a) Sasaki, T.; Minamoto, K.; Kino, M.; Mizuno, T. *J. Org. Chem.* **1976**, *41*, 1100. (b) Blank, H. U.; Wempen, I.; Fox, J. J. *J. Org. Chem.* **1969**, *35*, 1131. (c) Blank, H. U.; Fox, J. J. *J. Am. Chem. Soc.* **1968**, *90*, 7175.

(10) (a) Sasaki, T.; Minamoto, K.; Suzuki, T.; Sugiura, T. *J. Org. Chem.* **1979**, *4*, 1424. (b) Sasaki, T.; Minamoto, K.; Suzuki, T.; Sugiura, T. *J. Am. Chem. Soc.* **1978**, *100*, 2248. (c) Sasaki, T.; Minamoto, K.; Suzuki, T.; Yamashita, S. *Tetrahedron* **1980**, *36*, 865.

(11) (a) Kim, J. N.; Ryu, E. K. *Heterocycles* **1990**, *31*, 663. (b) Kim, J. N.; Ryu, E. K. *Synth. Commun.* **1990**, *20*, 1373. (c) Kim, J. N.; Ryu, E. K. *Heterocycles* **1990**, *31*, 1693.

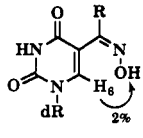
0022-3263/92/1957-1088$03.00/0

to the 5,6-double bond of pyrimidine nucleosides. We wish to report that, unusually, substitution products were obtained rather than cycloaddition products.

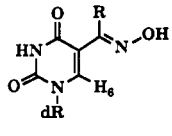
Results and Discussion

The 5-aroylpyrimdine nucleoside oximes **3–10** were prepared by the reaction of the corresponding nucleosides **2a–d** with nitrile oxides. The nitrile oxides were generated in situ by treating hydroximoyl chlorides **1a–e** with triethylamine at room temperature (Scheme I). Treatment of uridine (**2a**), 2′,3′,5′-tri-*O*-benzoyluridine (**2b**), 3′,5′-di-*O*-acetyl-2′-deoxyuridine (**2c**), or 2′-deoxyuridine (**2d**) with 2,6-dichlorobenzohydroximoyl chloride (**1a**) in DMF/THF at room temperature gave the corresponding pyrimidine nucleoside oximes **3–6** in yields of 49–83%. The reaction of 2′-deoxyuridine (**2d**) with the other halogen-substituted benzohydroximoyl chlorides, **1b–e**, under the same conditions gave the oximes **7–10** in yields of 43–89%. The results are summarized in Table I. TLC analysis of the reaction mixtures after 3 days showed the presence of the desired oximes **3–10**, the unreacted nucleosides **2a–d**, and small amounts of unidentified nonpolar materials. The unidentified materials were believed to be mixtures of unreacted nitrile oxide and the corresponding furoxan, the nitrile oxide dimer.[12] Column chromatography on silica gel gave the pure products **3–10** in yields of 43–89%.

The structures of compounds **3–10** were established by ^{1}H NMR spectroscopy, fast-atom bombardment mass spectrometry, and elemental analysis. The ^{1}H NMR spectra showed singlets due to the oxime protons and the C-6 protons in the regions 12.07–12.50 ppm and 8.46–8.92 ppm, respectively. Signals due to the C-5 protons of the starting materials were not present. The configuration of the oxime group was established by NOE experiments performed at 300 MHz. Compound **10** dissolved in DMSO-d_6 served as a model compound. Thus, irradiation of the 6-H proton signal gave a ca. 2% enhancement of the oxime proton signal. These observations[13] and the presence of two signals at 8.92 (6-H) and 12.27 ppm (oxime proton) in NMR spectrum[14] led to the unequivocal assignment of the *Z* configuration to compounds **3–10**. Such a structure is consistent with the mechanism proposed for the reaction (vide infra).



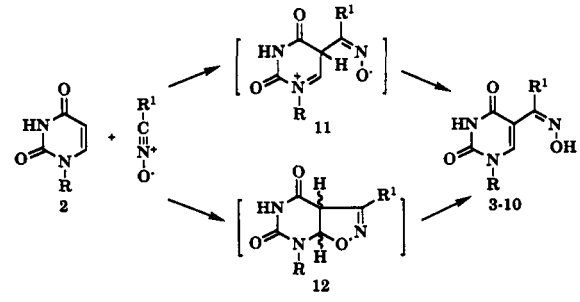
Z-10



E-10

It was interesting that no 1,3-cycloaddition products were detected in the reaction mixtures by TLC. Competition between 1,3-addition and cycloaddition has been observed in a few cases, as previously described. 1,3-Addition products have been obtained from the reactions of nitrile imines with strongly nucleophilic heteroaromatics like substituted imidazoles and benzimidazoles.[15] Competition between 1,3-addition and cycloaddition has also been observed in the reactions of nitrile imines with heteroaromatics like indole[16] and pyrrole.[17] However, there appear to be no reported instances in which only 1,3-addition products were observed in the reactions of nitrile oxides with dipolarophiles.

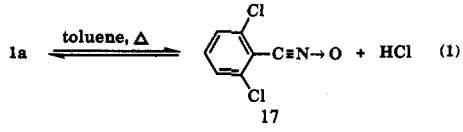
Scheme II[a]



[a] R = ribosyl or 2′-deoxyribosyl. R^1 = substituted phenyl.

Two mechanisms for the formation of the 1,3-addition products **3–10** seem to be plausible (Scheme II). Thus, electrophilic attack by the nitrile oxide on the 5-position of **2** could form intermediate **11**. A hydrogen transfer from carbon to oxygen would give **3–10**.[3a,5,6,18] Alternatively, a concerted 1,3-dipolar cycloaddition of the nitrile oxide to the 5,6-double bond of **2** could form intermediate **12**. Ring opening of **12** could yield products **3–10**.[19]

The reaction of a model compound, 1,3-dimethyluracil (**13**) with 2,6-dichlorobenzonitrile oxide—generated in different ways from 2,6-dichlorobenzohydroximoyl chloride (**1a**)—was examined to gain additional evidence that might be valuable in elucidating the mechanism (Scheme III). Thus, treatment of a mixture of **1a** and **13** with triethylamine at room temperature for 3 days afforded only the 1,3-addition product **14** (pathway a). On the other hand, thermally generated[20] 2,6-dichlorobenzonitrile oxide gave the dihydroisoxazolopyrimidine[21] derivative **15** instead of **14** (pathway b). The structures of **14** and **15** were easily differentiated by ^{1}H NMR spectroscopy. In the spectrum of **14**, a singlet due to the oxime proton appeared at 12.10 ppm and a singlet due to the C-6 proton appeared at 8.63 ppm. In the spectrum of **15**, a doublet due to the C-9 proton appeared at 4.17 ppm and a doublet due to the C-8 proton appeared at 4.78 ppm. Both had an identical coupling constant, J = 9.3 Hz.[22] The use of dry toluene as a solvent and a nirogen stream, which is required to remove the liberated HCl from **1a** (eq 1),[20] were needed to obtain **15** as the major product. Otherwise, in the case



(12) (a) Gasco, A.; Boulton, A. J. *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1981; Vol. 29, p 251. (b) Kaufman, J. V. R.; Picard, J. P. *Chem. Rev.* **1959**, *59*, 429.

(13) (a) Heinisch, G.; Holzer, W. *Tetrahedron Lett.* **1990**, *31*, 3109. (b) Howe, R. K.; Shelton, B. R. *J. Org. Chem.* **1990**, *55*, 4603.

(14) (a) Park, J. S.; Chang, C. T.-C.; Schmidt, C. L.; Golander, Y.; De Clercq, E.; Descamps, J.; Mertes, M. P. *J. Med. Chem.* **1980**, *23*, 661. (b) Kleinspehn, G. G.; Jung, J. A.; Studniarz, S. A. *J. Org. Chem.* **1967**, *32*, 460.

(15) (a) Croce, P. D.; Ioannisci, M.; Licandro, E. *J. Chem. Soc., Perkin Trans. 1* **1979**, 330. (b) Ruccia, M.; Vivona, N.; Cusmano, G.; Marino, M. L. *Gazz. Chim. Ital.* **1970**, *100*, 358.

(16) (a) Laude, B.; Soufiaoui, M.; Arriau, J. *J. Heterocycl. Chem.* **1977**, *14*, 1183. (b) Ruccia, M.; Vivona, N.; Cusmano, G.; Marino, M. L.; Piozzi, F. *Tetrahedron* **1973**, *29*, 3159.

(17) (a) Ruccia, M.; Vivona, N.; Cusmano, G. *J. Heterocycl. Chem.* **1978**, *15*, 293. (b) Ruccia, M.; Vivona, N.; Cusmano, G.; Macaluso, G. *J. Heterocycl. Chem.* **1978**, *15*, 1485.

(18) Gibert, J. P.; Petrus, C.; Petrus, F. *J. Heterocycl. Chem.* **1979**, *16*, 311.

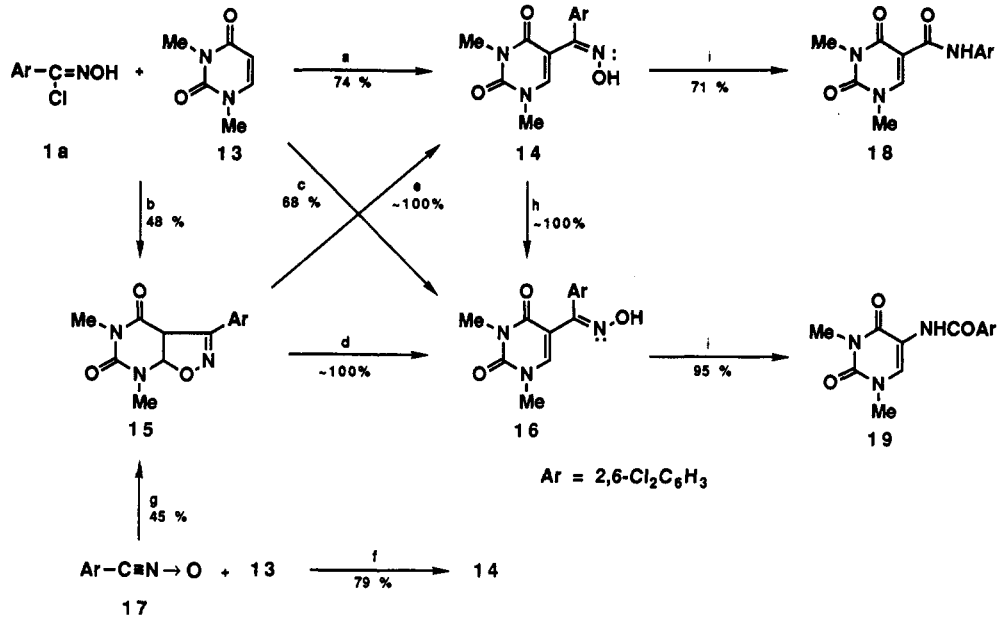
(19) Reinhoudt, D. N.; Kouwenhoven, C. G. *Recl. J. Neth. Chem. Soc.* **1974**, *93*, 321.

(20) (a) Sasaki, T.; Yoshioka, T. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 258. (b) Caldirola, P.; Amici, M. DE.; Micheli, C. DE. *Heterocycles* **1985**, *23*, 2479.

(21) Tuman, W. J.; Bauer, L. *J. Org. Chem.* **1972**, *37*, 2983.

(22) The magnitude of the coupling constant (J = 9.25 Hz) is in good agreement with the magnitude of the cis coupling constant established for a series of 3-phenyl-2-isoxazolines. See: Sustmann, R.; Huisgen, R.; Huber, H. *Chem. Ber.* **1967**, *100*, 1802.

Scheme III[a]



[a] (a) Et_3N/THF, rt, 3 days; (b) dry toluene, reflux (N_2 stream), 3 days; (c) toluene, reflux, 3 days; (d) toluene, HCl (cat.), reflux, 10 h; (e) Et_3N/THF, rt, 24 h or DMF, rt, 24 h; (f) DMF, rt, 3 days; (g) toluene, rt, 3 days; (h) aqueous EtOH, concd HCl, 50–60 °C, 10 h; (i) $SOCl_2/Et_2O$, rt, 10 h.

of using reagent-grade toluene which may contain some moisture or no nitrogen stream, we could obtain the *E* isomer **16** as the major product (pathway c). Interestingly, we found that the cycloaddition product **15** is very susceptible to acid, base, or even polar solvents. For example, **15** was converted easily and quantitatively to **16** by treatment with HCl in refluxing toluene (pathway d). Treatment of **15** with Et_3N in THF or simply dissolving in DMF at room temperature cleanly afforded the *Z* isomer **14** within 1 day (pathway e). In addition, the reaction of isolated 2,6-dichlorobenzonitrile oxide (**17**)[11b] with **13** in DMF as solvent in the absence of acid or base produced **14** in good yield (pathway f), whereas the cycloaddition product **15** could be obtained in a nonpolar solvent such as toluene (pathway g). *Z* isomer **14** was converted quantitatively to the more stable *E* isomer **16** by being warmed in aqueous ethanol containing HCl within 10 h (pathway h). The stereochemistry of **14** and **16** could be easily confirmed from their ^1H NMR spectra and chemical transformation using Beckmann rearrangement[23] (pathway i). The oxime protons appeared at 12.10 and 11.54 ppm, and the C-6 protons appeared at 8.63 and 8.09 ppm for **14** and **16**, respectively. The *Z* isomer **14** was converted to **18** in 71% yield by treatment with $SOCl_2$, and its structure was confirmed from the peak at $m/z = 167$ corresponding to the [1,3-Me_2-uracil − CO]$^{+\cdot}$. The *E* isomer **16** was converted to **19** in 95% yield by treatment with $SOCl_2$, and, in this case, the base peak appeared at $m/z = 173$ corresponded to [ArCO]$^{+\cdot}$. From these results, we could strongly suggest that the 1,3-addition products **3–10** were formed by the ring-opening reaction of the dihydroisoxazolopyrimidine derivative **12** that initially formed via [3 + 2] dipolar cycloaddition reactions. The same evidence rules out the pathway that involves intermediate **11** (see Scheme II).

The reactivity of the 5,6-double bond of pyrimidines toward some less stable nitrile oxides[24] was also examined.

Scheme IV

1f:	R^1=4-ClC_6H_4	**20** 20%
1g:	R^1=C_6H_5	no reaction
1h:	R^1=EtO_2C	no reaction

1,3-Dimethyluracil (**13**) served as a model compound (Scheme IV). The reaction of 4-chlorobenzonitrile oxide (generated from **1f**) gave a low yield of **20**. Less stable benzonitrile oxide (from **1g**) and carbethoxyformonitrile oxide (from **1h**) did not give any of the desired products. Only starting materials and furoxan were isolated from the reaction of **13** with **1g** or **1h**. These results indicate that the dipolarophilicity of the 5,6-double bond of uracil derivatives toward the less stable nitrile oxides is too low to give products of 1,3-addition.

In conclusion, it has been demonstrated that the reaction of uracil nucleosides with some stable nitrile oxides cleanly gave products of 1,3-addition in which the configuration of the oxime group was shown to be *Z* by ^1H NMR and NOE studies. The formation of 1,3-addition products was explained as being the result of ring-opening of the initially formed 1,3-cycloaddition product. In view of the biological importance of 5-substituted pyrimidine nucleosides, the application of the reactions described here could be useful in synthetic pyrimidine nucleoside chemistry. Further studies of the reaction of nitrile oxides with other pyrimidine nucleosides and of the biological activity of the products is underway.

Experimental Section

Melting points were measured with a Thomas-Hoover melting point apparatus and are uncorrected. ^1H NMR spectra were recorded with a Bruker AM-300 spectrometer. TMS served as the internal standard. Electron impact mass spectra were recorded with a Shimadzu QP 1000 and fast-atom bombardment mass spectra were recorded with a JEOL JMS-DX-303 instrument. UV spectra were recorded with a Shimadzu UV-265 instrument.

(23) Gawley, R. E. *Org. React.* **1988**, *35*, 1.
(24) (a) Grundmann, C.; Dean, J. M. *J. Org. Chem.* **1965**, *30*, 2809. (b) Grundmann, C.; Richter, R. *J. Org. Chem.* **1967**, *32*, 2308. (c) Quilico, A. *Experientia* **1970**, *26*, 1169.

Elemental analyses (C, H, and N) were performed with Perkin-Elmer 240 C elemental analyzer. Thin layer chromatography (TLC) was performed with precoated silica gel plates (Kieselgel 60F-254, Merck). Column chromatography was performed with Merck silica gel 60 (230–400-mesh ASTM).

Uridine (**2a**) and 2′-deoxyuridine (**2d**) were purchased from Aldrich and were used as received. 1,3-Dimethyluracil (**13**),[25] 2′,3′,5′-tri-*O*-benzoyluridine (**2b**),[26] and 3′,5′-di-*O*-acetyl-2′-deoxyuridine (**2c**)[27] were prepared according to the literature. All the starting materials were characterized by mp, MS, and ^{1}H NMR. Ethyl chlorooximidoacetate was purchased from Aldrich. All the other hydroximoyl chlorides were prepared from the corresponding aldoximes by treatment with NCS in DMF[28] and were used without further purification.

5-(2,6-Dichlorobenzoyl)uridine Oxime (3). To a stirred solution of **2a** (2.44 g, 10 mmol), **1a** (2.92 g, 13 mmol) in dry DMF (5 mL), and THF (5 mL) was added, drop-by-drop, Et_3N (1.31 g, 13 mmol) in THF (5 mL) over 2 h. The mixture was stirred at room temperature for 3 days. After removal of the precipitate by filtration, the low-boiling materials were evaporated in vacuo. The oily residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 99:1, then 86:14) to give **3** as a white solid (2.16 g, 50%): TLC R_f = 0.64 ($CHCl_3$/MeOH, 7:3); UV λ_{max} (MeOH) 281 nm; ^{1}H NMR (DMSO-d_6) δ 3.53 (m, 2 H, H-5′,5″), 3.90 (m, 2 H, H-3′,4′), 4.03 (m, 1 H, H-2′), 4.97 (t, J = 5.0 Hz, 1 H, OH, D_2O-exchangeable), 5.18 (d, J = 4.86 Hz, 1 H, OH, D_2O-exchangeable), 5.53 (d, J = 5.61 Hz, 1 H, OH, D_2O-exchangeable), 5.85 (d, J = 5.25 Hz, 1 H, H-1′), 7.32–7.47 (m, 3 H, Ar), 8.73 (s, 1 H, H-6), 11.47 (br s, 1 H, NH, D_2O-exchangeable), 12.10 (s, 1 H, oxime proton, D_2O-exchangeable); FABMS, 432 (MH^+). Anal. Calcd for $C_{16}H_{15}N_3O_7Cl_2 \cdot {}^1/_2H_2O$: C, 43.56; H, 3.65; N, 9.52. Found: C, 43.44; H, 4.00; N, 9.31.

5-(2,6-Dichlorobenzoyl)-2′,3′,5′-tri-*O*-benzoyluridine oxime (4) was prepared from **2b** (5.56 g, 10 mmol) and **1a** (2.92 g, 13 mmol) in the manner described above for the preparation of **3**. Column chromatography on silica gel (petroleum ether, then Et_2O) gave **4** as a white solid (6.17 g, 83%): TLC R_f = 0.91 ($CHCl_3$/MeOH, 7:3); UV λ_{max} (MeOH) 274, 277 nm; ^{1}H NMR (DMSO-d_6) δ 4.57–4.72 (m, 2 H, H-5′,5″), 4.78–4.83 (m, 1 H, H-4′), 5.95–6.00 (m, 1 H, H-3′), 6.04–6.08 (m, 1 H, H-2′), 6.32 (d, J = 3.96 Hz, 1 H, H-1′), 7.32–8.04 (m, 18 H, Ar), 8.77 (s, 1 H, H-6), 11.71 (br s, 1 H, NH), 12.22 (s, 1 H, oxime proton); FABMS, 744 (MH^+). Anal. Calcd for $C_{37}H_{27}N_3O_{10}Cl_2 \cdot {}^1/_2H_2O$: C, 58.98; H, 3.75; N, 5.58. Found: C, 58.87; H, 3.59; N, 5.60.

5-(2,6-Dichlorobenzoyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine oxime (5) was prepared from **2c** (3.12 g, 10 mmol) and **1a** (2.92 g, 13 mmol) in the manner described above for the preparation of **3**. Column chromatography on silica gel (hexane, then Et_2O) gave **5** as a white solid (3.24 g, 65%): TLC R_f = 0.87 ($CHCl_3$/MeOH, 7:3); UV λ_{max} (MeOH) 281 nm; ^{1}H NMR (DMSO-d_6) δ 2.03 (s, 3 H, acetyl), 2.08 (s, 3 H, acetyl), 2.28–2.53 (m, 2 H, H-2′,2″), 4.19 (m, 2 H, H-5′,5″), 4.30 (m, 1 H, H-4′), 5.23 (m, 1 H, H-3′), 6.20 (dd, $J_{H\text{-}1'\text{-}H\text{-}2',H\text{-}2''}$ = 7.8 and 6.19 Hz, 1 H, H-1′), 7.32–7.46 (m, 3 H, Ar), 8.67 (s, 1 H, H-6), 11.55 (br s, 1 H, NH), 12.19 (s, 1 H, oxime proton); FABMS, 500 (MH^+). Anal. Calcd for $C_{20}H_{19}N_3O_8Cl_2 \cdot {}^1/_2H_2O$: C, 47.17; H, 3.96; N, 8.25. Found: C, 47.18; H, 3.75; N, 8.43.

5-(2,6-Dichlorobenzoyl)-2′-deoxyuridine oxime (6) was prepared from **2d** (2.28 g, 10 mmol) and **1a** (2.92 g, 13 mmol) in the manner described above for the preparation of **3**. Column chromatography on silica gel ($CHCl_3$/MeOH, 90:10) gave **6** as a white solid (2.03 g, 49%): TLC R_f = 0.74 ($CHCl_3$/MeOH, 7:3); UV λ_{max} (MeOH) 282 nm; ^{1}H NMR (DMSO-d_6) δ 2.05–2.35 (m, 2 H, H-2′,2″), 3.49 (m, 2 H, H-5′,5″), 3.83 (m, 1 H, H-4′), 4.20 (m, 1 H, H-3′), 4.94 (t, J = 5.22 Hz, 1 H, OH), 5.35 (d, J = 4.09 Hz, 1 H, OH), 6.18 (t, J = 6.55 Hz, 1 H, H-1′), 7.34–7.46 (m, 3 H, Ar), 8.73 (s, 1 H, H-6), 11.46 (br s, 1 H, NH), 12.11 (s, 1 H, oxime $C_{16}H_{15}N_3O_6Cl_2 \cdot H_2O$: C, 44.26; H, 3.94; N, 9.68. Found: C, 44.40; H, 3.79; N, 9.76.

5-(2-Chloro-6-fluorobenzoyl)-2′-deoxyuridine oxime (7) was prepared from **2d** (2.28 g, 10 mmol) and **1b** (2.71 g, 13 mmol) in the manner described above for the preparation of **3**. Column chromatography on silica gel ($CHCl_3$/MeOH, 90:10) gave **7** as a white solid (2.39 g, 60%): TLC R_f = 0.73 ($CHCl_3$/MeOH, 7:3); UV λ_{max} (MeOH) 275 nm; ^{1}H NMR (DMSO-d_6) δ 2.02–2.24 (m, 2 H, H-2′,2″), 3.51 (m, 2 H, H-5′,5″), 3.83 (m, 1 H, H-4′), 4.22 (m, 1 H, H-3′), 4.95 (t, J = 4.52 Hz, 1 H, OH), 5.33 (d, J = 3.83 Hz, 1 H, OH), 6.19 (t, J = 6.32 Hz, 1 H, H-1′), 7.19–7.44 (m, 3 H, Ar), 8.58 (s, 1 H, H-6), 11.48 (br s, 1 H, NH), 12.07 (s, 1 H, oxime proton); FABMS, 400 (MH^+). Anal. Calcd for $C_{16}H_{15}N_3O_6FCl \cdot H_2O$: C, 45.99; H, 4.10; N, 10.06. Found: C, 45.90; H, 4.01; N, 10.01.

5-(2,6-Difluorobenzoyl)-2′-deoxyuridine oxime (8) was prepared from **2d** (2.28 g, 10 mmol) and **1c** (2.49 g, 13 mmol) in the manner described above for the preparation of **3**. Column chromatography on silica gel ($CHCl_3$/MeOH, 90:10) gave **8** as a white solid (2.72 g, 71%): TLC R_f = 0.56 ($CHCl_3$/MeOH, 7:3); UV λ_{max} (MeOH) 271 nm; ^{1}H NMR (DMSO-d_6) δ 2.02–2.23 (m, 2 H, H-2′,2″), 3.52 (m, 2 H, H-5′,5″), 3.82 (m, 1 H, H-4′), 4.22 (m, 1 H, H-3′), 4.97 (t, J = 4.96 Hz, 1 H, OH), 5.31 (d, J = 4.09 Hz, 1 H, OH), 6.19 (t, J = 6.55 Hz, 1 H, H-1′), 7.04–7.48 (m, 3 H, Ar), 8.46 (s, 1 H, H-6), 11.52 (br s, 1 H, NH), 12.08 (s, 1 H, oxime proton); FABMS, 384 (MH^+). Anal. Calcd for $C_{16}H_{15}N_3O_6F_2 \cdot H_2O$: C, 47.89; H, 4.27; N, 10.47. Found: C, 48.44; H, 4.29; N, 10.54.

5-(2,3,5,6-Tetrafluorobenzoyl)-2′-deoxyuridine oxime (9) was prepared from **2d** (2.28 g, 10 mmol) and **1d** (2.96 g, 13 mmol) in the manner described above for the preparation of **3**. Column chromatography on silica gel ($CHCl_3$/MeOH, 90:10) gave **9** as a white solid (1.80 g, 43%): TLC R_f = 0.62 ($CHCl_3$/MeOH, 7:3); UV λ_{max} (MeOH) 274 nm; ^{1}H NMR (DMSO-d_6) δ 2.05–2.26 (m, 2 H, H-2′,2″), 3.52 (m, 2 H, H-5′,5″), 3.83 (m, 1 H, H-4′), 4.24 (m, 1 H, H-3′), 4.99 (t, J = 5.08 Hz, 1 H, OH), 5.32 (d, J = 4.18 Hz, 1 H, OH), 6.18 (t, J = 6.48 Hz, 1 H, H-1′), 7.88–7.96 (m, 1 H, Ar), 8.64 (s, 1 H, H-6), 11.62 (br s, 1 H, NH), 12.50 (s, 1 H, oxime proton); FABMS, 420 (MH^+). Anal. Calcd for $C_{16}H_{13}N_3O_6F_4 \cdot {}^1/_2H_2O$: C, 44.87; H, 3.29; N, 9.81. Found: C, 44.65; H, 3.08; N, 9.49.

5-(2,3,6-Trichlorobenzoyl)-2′-deoxyuridine oxime (10) was prepared from **2d** (2.28 g, 10 mmol) and **1e** (3.37 g, 13 mmol) in the manner described above for the preparation of **3**. Column chromatography on silica gel ($CHCl_3$/MeOH, 90:10) gave **10** as a white solid (4.00 g, 89%): TLC R_f = 0.73 ($CHCl_3$/MeOH, 7:3); UV λ_{max} (MeOH) 288 nm; ^{1}H NMR (DMSO-d_6) δ 2.04–2.23 (m, 2 H, H-2′,2″), 3.42–3.53 (m, 2 H, H-5′,5″), 3.84 (m, 1 H, H-4′), 4.22 (m, 1 H, H-3′), 4.94 (t, J = 5.29 Hz, 1 H, OH, D_2O-exchangeable), 5.34 (d, J = 4.18 Hz, 1 H, OH, D_2O-exchangeable), 6.18 (t, J = 6.50 Hz, 1 H, H-1′), 7.48 (d, J = 8.7 Hz, 1 H, Ar), 7.64 (d, J = 8.7 Hz, 1 H, Ar), 8.92 (s, 1 H, H-6), 11.49 (br s, 1 H, NH, D_2O-exchangeable), 12.27 (s, 1 H, oxime proton, D_2O-exchangeable); FABMS, 450 (MH^+). Anal. Calcd for $C_{16}H_{14}N_3O_6Cl_3 \cdot H_2O$: C, 41.00; H, 3.44; N, 8.97. Found: C, 40.61; H, 3.19; N, 8.95.

1,3-Dimethyl-5-(2,6-dichlorobenzoyl)uracil Oxime (14) from 1a and 13. To a stirred solution of **13** (1.40 g, 10 mmol) and **1a** (2.25 g, 10 mmol) in dry THF (50 mL) was added, drop-by-drop, Et_3N (1.10 g, 11 mmol) in THF (10 mL) over 1 h. The mixture was stirred at room temperature for 3 days. After removal of the precipitate by filtration, the filtrate was evaporated to dryness in vacuo in the presence of silica gel (8 g). Column chromatography on silica gel (CH_2Cl_2, then Et_2O) gave the desired product as a white solid (2.42 g, 74%): TLC R_f = 0.63 (Et_2O); mp 215–217 °C; ^{1}H NMR (DMSO-d_6) δ 3.07 (s, 3 H), 3.41 (s, 3 H), 7.30–7.45 (m, 3 H, Ar), 8.63 (s, 1 H, H-6), 12.10 (s, 1 H, oxime proton); EIMS (70 eV) m/z (rel intensity) 42 (71), 194 (22), 292 (base), 293 (18), 294 (36), 328 (M^+ + 1, 10). Anal. Calcd for $C_{13}H_{11}N_3O_3Cl_2$: C, 47.58; H, 3.38; N, 12.80. Found: C, 47.42; H, 3.38; N, 12.77.

14 from 13 and 17. A solution of **13** (420 mg, 3 mmol) and **17** (565 mg, 3 mmol) in DMF (2 mL) was stirred at room temperature for 3 days. The reaction mixture was purified by column chromatography on silica gel (hexane/CH_2Cl_2, 1:1, then Et_2O) and afforded desired product **14** as a white solid (775 mg, 79%).

3-(2,6-Dichlorophenyl)-5,7-dimethyl-8,9-dihydroisoxazolo[5,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (15) from 1a and

(25) Johnson, T. B.; Clapp, S. H. *J. Biol. Chem.* **1909**, (5), 49; *Chem. Abstr.* **1909**, *3*, 2147.

(26) Fox, J. J.; Praag, D. V.; Wempen, I.; Doerr, I. L.; Cheong, L.; Knoll, J. E.; Eidinoff, M. L.; Bendich, A.; Brown, G. B. *J. Am. Chem. Soc.* **1959**, *81*, 178.

(27) Robins, M. J.; MacCoss, M.; Naik, S. R.; Ramani, G. *J. Am. Chem. Soc.* **1976**, *98*, 7381.

(28) Liu, K.-C.; Shelton, B. R.; Howe, R. K. *J. Org. Chem.* **1980**, *45*, 3916.

13. A stirred solution of **1a** (1.13 g, 5 mmol) and **13** (0.70 g, 5 mmol) in dry toluene (50 mL) was heated to reflux for 3 days under a gentle stream of N_2 to remove the liberated HCl. After evaporation of the solvent in vacuo, column chromatographic purification on silica gel (CH_2Cl_2) afforded pure product **15** as a white solid (785 mg, 48%): TLC R_f = 0.52 (Et_2O); mp 187–188 °C, resolidify, 211–215 °C dec; ^1H NMR (C_6D_6) δ 2.79 (s, 3 H), 3.07 (s, 3 H), 4.17 (d, J = 9.3 Hz, 1 H, H-9), 4.78 (d, J = 9.3 Hz, 1 H, H-8), 6.32 (t, J = 8.1 Hz, 1 H, Ar), 6.71 (d, J = 8.1 Hz, 2 H, Ar); ^1H NMR (MeOH-d_4/acetone-d_6, 1:1) δ 3.09 (s, 3 H), 3.15 (s, 3 H), 4.94 (d, J = 9.25 Hz, 1 H, H-9), 6.12 (d, J = 9.25 Hz, 1 H, H-8), 7.51 (s, 3 H, Ar); EIMS (20 eV) m/z (rel intensity) 83 (52), 140 (base), 292 (44), 327 (M^+, 5). Anal. Calcd for $C_{13}H_{11}N_3O_3Cl_2$: C, 47.58; H, 3.38; N, 12.80. Found: C, 47.33; H, 3.29; N, 12.75.

15 from 13 and 17. A solution of **13** (420 mg, 3 mmol) and **17** (565 mg, 3 mmol) in dry toluene (30 mL) was stirred at room temperature for 3 days during which time crystalline product **15** appeared in the reaction mixture. The solid was separated by filtration, washed with toluene (1 mL), and dried in vacuo to give the pure product **15** (290 mg). Additional product (152 mg) was obtained from the filtrates and washings in a manner similar to that used for the preparation of **15** from **1a** and **13**. Overall yield of **15** was 442 mg (45%).

Transformation of 15 to 14. To a stirred solution of **15** (100 mg, 0.3 mmol) in THF (8 mL) was added triethylamine (50 mg, 0.5 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 day, and the low-boiling materials were removed under reduced pressure to give **14** (100 mg, 100%).

1,3-Dimethyl-5-(2,6-dichlorobenzoyl)uracil Oxime (16). A stirred solution of **1a** (2.25 g, 10 mmol) and **13** (1.40 g, 10 mmol) in reagent-grade toluene (50 mL) was heated to reflux for 3 days. After evaporation of the solvent in vacuo, the solid residue was washed with Et_2O (3 × 10 mL). Recrystallization from toluene gave **16** as white flakes (2.23 g, 68%): TLC R_f = 0.50 (Et_2O); mp 212–214 °C dec; ^1H NMR (DMSO-d_6) δ 3.08 (s, 3 H), 3.41 (s, 3 H), 7.14–7.44 (m, 3 H, Ar), 8.09 (s, 1 H, H-6), 11.54 (s, 1 H, oxime proton); EIMS (20 eV) m/z (rel intensity) 292 (base), 294 (44), 327 (M^+, 6), 329 (4). Anal. Calcd for $C_{13}H_{11}N_3O_3Cl_2$: C, 47.58; H, 3.38; N, 12.80. Found: C, 47.68; H, 3.41; N, 12.77.

Transformation of 14 to 16. To a stirred suspension of **14** (100 mg, 0.3 mmol) in 50% aqueous ethanol (20 mL) was added concd HCl (0.5 mL), and the reaction mixture was heated to 50–60 °C for 10 h. TLC analysis showed complete conversion of **14** to **16**.

Transformation of 15 to 16. **15** (330 mg, 1 mmol) was suspended in toluene (200 mL) and heated to reflux under a gentle stream of HCl, during which time **15** was cleanly converted to **16** (TLC analysis). Evaporation of the solvent after 10 h gave a white solid (330 mg, 100%), which was identical to **16** in all respects (TLC, mp, and MS).

***N*-(2,6-Dichlorophenyl)-1,3-dimethyl-5-uracilcarboxamide (18).** To a stirred solution of **14** (200 mg, 0.61 mmol) in dry Et_2O (10 mL) was added, drop-by-drop, $SOCl_2$ (0.30 mL, 4.0 mmol) over 10 min at 0 °C. The mixture was stirred at room temperature for 10 h. The reaction mixture was poured into cold water (50 mL) and extracted with EtOAc (2 × 50 mL). The organic layers were combined and washed with water (50 mL), dried with $MgSO_4$, and evaporated to dryness in vacuo. Column chromatography of the residue on silica gel (Et_2O) afforded pure product as a white solid (141 mg, 71%): TLC R_f = 0.41 (Et_2O); mp 262–264 °C dec; ^1H NMR (DMSO-d_6) δ 3.29 (s, 3 H), 3.48 (s, 3 H), 7.30–7.65 (m, 3 H, aromatic), 8.72 (s, 1 H, H-6), 10.61 (brs, 1 H, NH); EIMS (20 eV) m/z (rel intensity) 43 (29), 167 (91), 292 (base), 328 (M^+ + 1, 1). Anal. Calcd for $C_{13}H_{11}N_3O_3Cl_2$: C, 47.58; H, 3.38; N, 12.80. Found: C, 47.83; H, 3.49; N, 12.75.

***N*-(2,6-Dichlorobenzoyl)-1,3-dimethyl-5-aminouracil (19).** To a stirred solution of **16** (150 mg, 0.45 mmol) in dry Et_2O (10 mL) was added, drop-by-drop, $SOCl_2$ (0.22 mL, 3.0 mmol) over 10 min at 0 °C. The mixture was stirred at room temperature for 10 h. Product **19** was separated from the reaction mixture in a manner similar to that used for the preparation of **18**, as a white solid (143 mg, 95%): TLC R_f = 0.60 (Et_2O); mp 211–212 °C dec; ^1H NMR (DMSO-d_6) δ 3.24 (s, 3 H), 3.39 (s, 3 H), 7.35–7.60 (m, 3 H, Ar), 8.48 (s, 1 H, H-6), 10.21 (br s, 1 H, NH); EIMS (20 eV) m/z (rel intensity) 173 (base), 175 (70), 327 (M^+, 55), 329 (36). Anal. Calcd for $C_{13}H_{11}N_3O_3Cl_2$: C, 47.58; H, 3.38; N, 12.80. Found: C, 47.69; H, 3.50; N, 12.63.

1,3-Dimethyl-5-(4-chlorobenzoyl)uracil Oxime (20). Compound **20** was prepared in a manner similar to that used for the preparation of **14**. **20**: white solid (0.60 g, 20%); TLC R_f = 0.46 (Et_2O); mp 245–246 °C dec; ^1H NMR (DMSO-d_6) δ 3.18 (s, 3 H), 3.35 (s, 3 H), 7.40–7.60 (m, 4 H, Ar), 7.84 (s, 1 H, H-6), 11.66 (s, 1 H, oxime proton); EIMS (70 eV) m/z (rel intensity) 44 (base), 140 (15), 276 (14), 292 (14), 293 (M^+, 14), 294 (7), 295 (M^+ + 2, 5). Anal. Calcd for $C_{13}H_{12}N_3O_3Cl$: C, 53.16; H, 4.12; N, 14.31. Found: C, 53.15; H, 4.12; N, 14.15.

Acknowledgment. We thank the Korea Science and Engineering Foundation for financial support. We also thank Dr. Sueg-Geun Lee for his help in performing the NOE experiments.

Nucleophilic Addition of 2′-Deoxynucleosides to the *o*-Quinone Methides 10-(Acetyloxy)- and 10-Methoxy-3,4-dihydro-9(2*H*)-anthracenone

Steven R. Angle* and Wenjin Yang

Department of Chemistry, University of California, Riverside, California 92521-0403

Received May 20, 1991

In an effort to understand the chemistry of quinone methides, two simple, *o*-quinone methides 10-(acetyloxy)- and 10-methoxy-3,4-dihydro-9(2*H*)-anthracenone (**3** and **4**) have been constructed and their reactions with 2′-deoxyguanosine and 2′-deoxyadenosine investigated. The quinone methides were stirred with 1.2 equiv of nucleoside in H_2O/CH_3CN to afford products of N(6) alkylation with deoxyadenosine (**3**, 38%; **4**, 16% yield) and N(2) alkylation with deoxyguanosine (**3**, 27%; **4**, 5% yield).

Introduction

Quinone methides have been proposed as intermediates in biosynthesis[1] and in the chemistry of quinonoid antitumor compounds.[2] For example, the anthracycline antitumor antibiotics, a class of complex natural products, are thought to derive at least some of their biological ac-

(1) For leading references to the proposed intermediacy of quinone methides in biosynthesis see: (a) Angle, S. R.; Turnbull, K. D. *J. Am. Chem. Soc.* **1990**, *112*, 3698. (b) Saul, S. J.; Sugumaran, M. *FEBS Lett.* **1991**, *279*, 145. (c) Sugumaran, M.; Semensi, V. *J. Biol. Chem.* **1991**, *266*, 6073. (d) Gottlieb, O. R. *Fortsch. Chem. Org. Naturst.* **1978**, *35*, 1.

(2) General reviews and leading references: (a) Moore, H. W. *Science* **1977**, *197*, 527. (b) Moore, H. W.; Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249. (c) Abdella, B. R. J.; Fisher, J. F. *EHP, Environ. Health Perspect.* **1985**, *64*, 3. (d) Powis, G. *Pharmacol. Ther.* **1987**, *35*, 57. (e) Lin, A. J.; Sartorelli, A. C. *J. Med. Chem.* **1976**, *19*, 1336. (f) Lin, T.-S.; Antonini, I.; Cosby, L. A.; Sartorelli, A. C. *J. Med. Chem.* **1984**, *27*, 813. (g) Guadiano, G.; Koch, T. D. *Chem. Res. Toxicol.* **1991**, *4*, 2.

0022-3263/92/1957-1092$03.00/0