FACILE SYNTHESIS OF 2'-DEOXY-2'-ARYLTHIOURIDINES

Akira Matsuda and Tadashi Miyasaka*
School of Pharmaceutical Sciences, Showa University,
Hatanodai 1-5-8, Shinagawa-ku, Tokyo 142, Japan

Abstract---Cleavage of the anhydro linkage of O^2,2'-cyclouridine(1a) with o-,m-, and p-substituted thiophenols and β-naphthalenethiol was carried out in dimethylformamide to give the corresponding 2'-deoxy-2'-arylthiouridines(6a-g) in good yields.

Modification of the sugar moiety of nucleoside, especially at the 2'-position, is of increasing importance for the rational design of biochemically and pharmacologically interesting nucleoside analogs. We are interested in preparing nucleosides containing a sulfur function at sugar portion, because it is well-known that the sulfur atom has the stabilizing effect of the α-carbanion and α-carbocation. The application of the sulfur-stabilizing anion and cation chemistry to the nucleoside field would provide a new type of modification in the sugar moiety of nucleoside.

Among several methods available for the preparation of 2'-modified pyrimidine nucleosides, the use of readily accessible O^2,2'-cyclouridine(1a) as a starting material would be the most convenient. Cleavage of 1 has been studied with various nucleophiles.[1] Brown et al. reported that treatment of 1a with a large excess of sodium ethanthiolate in dimethylformamide gave 1-β-D-(3-deoxy-3-ethylthioxylofuranosyl)uracil(3).[1a] The formation of the "up" ethylthio derivative(3) from 1a apparently proceeded via the 2',3'-anhydronucleoside(2). Intramolecular nucleophilic attack by the 3'-O^- group at C-2' of 1a with concomitant cleavage of the O^2,2'-anhydro linkage would give rise to the 2',3'-anhydro intermediate(2). Cleavage of the 2',3'-anhydro linkage via nucleophilic attack by the thiolate anion at C-3' of 2 would result in the formation of 3.

On the other hand, Imazawa et al. have reported[1b] that when 3',5'-di-O-acetyl-O^2,2'-cyclouridine(1b) was heated with thioacetic acid in dioxane, 2'-deoxy-2'-acetylthio-3',5'-di-O-acetyluridine(4) was obtained in 65% yield. When hydrogen halides[1c] or lithium azide together with benzoic acid as an acid catalyst[1d] were employed in this reaction, the similar mode of fission was observed. These results suggest that reagents which have both weakly acidic and strongly nucleophilic character should be effective to cleave the O^2,2'-anhydro linkage of 1a to give 2'-deoxyuridines bearing a suitable substituent at 2'-position, but not at 3'-position. We, therefore, choose aromatic thiols as suitable reagents to introduce sulfur functions to 2'-position of the sugar moiety.

When O^2,2'-cyclouridine(1a) was treated with 1.5 mol equiv. of thiophenol in dimethylformamide at reflux temperature for 7h,[2] only one nucleosidic product was isolated from the reaction mixture as crystals in 96% yield. This product was assigned as 2'-deoxy-2'-phenylthiouridine(6a) on the basis of the following data.

Combustion analyses and mass spectroscopic data(M^+,m/e 336) gave an empirical formula $C_{15}H_{16}N_2O_5S$. The maximum of UV absorption of this compound in MeOH was observed at 256 nm, indicating that modification of the sugar structure had occurred. The substitution site and its configuration were established the chemical shift of H-2' and the coupling constants in ^1H NMR analysis. The remarkable upfield shift of H-2' resonance(δ 3.84) as compared with that of usual uridine derivatives indicated that the phenylthio group was attached to the 2'-position. Since the sugar ring conformation of 2'-substituted nucleosides which have the ribo-configuration is preferentially the C-2'-endo form,[1b] the coupling constant at the anomeric proton in 6a should be similar to that of 2'-deoxy-2'-methylthiouridine(5, $J_{1',2'}$= 8.3 Hz) but not that of the 2'-arabino-epimer($J_{1',2'}$=6.8 Hz).[3] The $J_{1',2'}$ value for 6a is 9.3 Hz, which establishes its ribo-configuration.

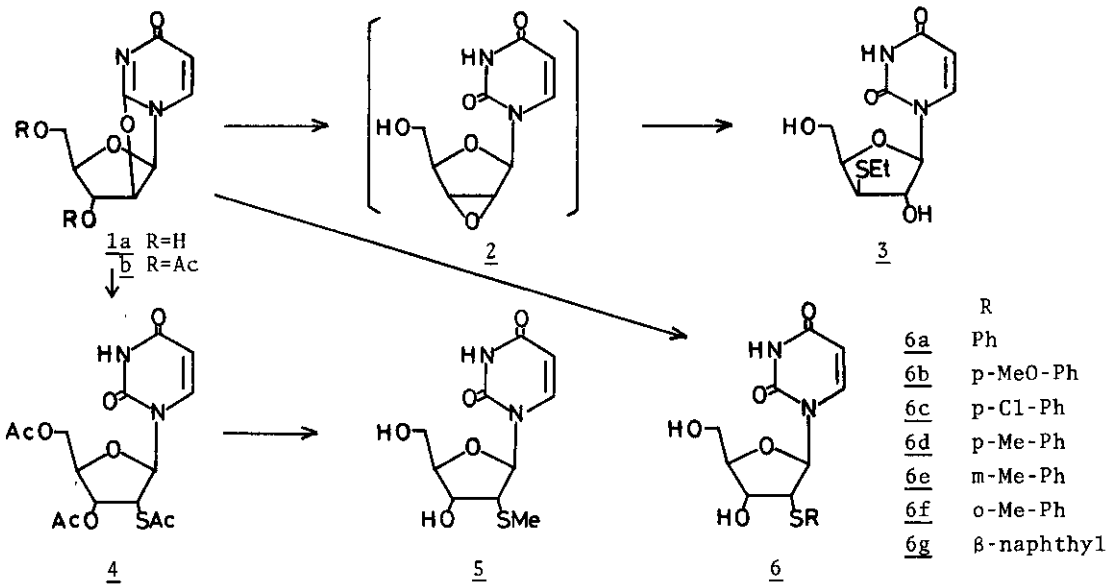

Table 1.

Reagent	Product	Reaction time (h)	Isolated yield (%)	Mp (°C)	Formula
PhSH	6a	7	96	205-6 a)	$C_{15}H_{16}N_2O_5S$
p-MeO-PhSH	6b	14	79	200-1	$C_{16}H_{18}N_2O_6S$
p-Cl-PhSH	6c	5	94	234-5	$C_{15}H_{15}ClN_2O_5S$
p-Me-PhSH	6d	10	90	221-2 b)	$C_{16}H_{18}N_2O_5S$
m-Me-PhSH	6e	11	62	195-6	$C_{16}H_{18}N_2O_5S$
o-Me-PhSH	6f	14	58	198-9	$C_{16}H_{18}N_2O_5S \cdot 0.5H_2O$
β-naphthyl-SH	6g	5	92	182-3	$C_{19}H_{18}N_2O_5S$

a) Ref.[2], mp 199-200°. b) Ref.[2], mp 212°.

Table 2. Proton Chemical Shifts(δ) and First-Order Coupling Constants(Hz) for 2'-Deoxy-2'-Arylthiouridines[a)]

Compd.	H-1'	H-2'	H-3'[b)]	H-4'	H-5'	H-5[b)]	H-6	Other
6a	6.18 (d $J_{1',2'}$=9.3)	3.84 (dd $J_{2',3'}$=4.9)	4.33 (t $J_{3',4'}$<1)	3.92 (m)	3.58 (m)	5.43 (dd $J_{5,6}$=8.3)	7.59 (d)	11.10(brs,NH), 5.87, 5.11(d,t,OH) 7.38-7.17(m,5H,Ph)
6b	6.17 (d $J_{1',2'}$=9.3)	c)	4.30 (t $J_{3',4'}$<1)	3.89 (m)	3.54 (m)	5.37 (dd $J_{5,6}$=8.3)	7.49 (d)	11.12(brs,NH), 5.80, 5.05(d,t,OH) 7.28, 6.77(d,d,4H,Ph), 3.69(s,Me)
6c	6.15 (d $J_{1',2'}$=8.8)	3.84 (dd $J_{2',3'}$=4.9)	4.35 (t $J_{3',4'}$<1)	3.91 (m)	3.59 (m)	5.49 (dd $J_{5,6}$=8.3)	7.61 (d)	11.13(brs,NH), 5.89, 5.10(d,t,OH) 7.31(m,4H,Ph)
6d	6.15 (d $J_{1',2'}$=9.3)	3.73 (dd $J_{2',3'}$=4.9)	4.31 (t $J_{3',4'}$<1)	3.92 (m)	3.55 (m)	5.41 (dd $J_{5,6}$=8.3)	7.54 (d)	11.07(brs,NH), 5.82, 5.08(d,t,OH) 7.22, 7.02(d,d,4H,Ph), 3.28(s,Me)
6e	6.18 (d $J_{1',2'}$=8.8)	3.79 (dd $J_{2',3'}$=5.1)	4.32 (t $J_{3',4'}$<1)	3.90 (m)	3.56 (m)	5.41 (dd $J_{5,6}$=8.3)	7.56 (d)	11.13(brs,NH), 5.86, 5.09(d,t,OH) 7.14-7.00(m,4H,Ph), 2.21(s,Me)
6f	6.17 (d $J_{1',2'}$=9.3)	3.72 (dd $J_{2',3'}$=5.1)	4.34 (t $J_{3',4'}$<1)	3.93 (m)	3.55 (m)	5.40 (dd $J_{5,6}$=8.3)	d)	11.13(brs,NH), 5.86, 5.12(d,t,OH) 7.35-7.02(m,4H,Ph), 2.34(s,Me)
6g	6.23 (d $J_{1',2'}$=8.8)	e)	4.36 (t $J_{3',4'}$<1)	3.97 (m)	3.60 (m)	5.39 (d $J_{5,6}$=8.3)	d)	7.82-7.35(m,7H,naphthyl)

a) Spectra were obtained on a JOEL JNM-FX 100 NMR spectrometer in Me_2SO-d_6 with Me_4Si as an internal standard. Chemical shift values are first order. Signals(in parentheses) are expressed as s, singlet; d, doublet; t, triplet; m, multiplet; dd, double doublet and br, broad. b) Appears as a doublet upon addition of D_2O in all the case. c) Overlapped with Me and H-5'. d) Overlapped with Ph protons. e) Overlapped with H-4'.

The analogous reaction of 1a with several o-, m-, and p-substituted thiophenols and β-naphthalenethiol was successfully carried out to give the respective compound 6b-g in good yields(see Table 1). Although the reaction time in Table 1 does not quantitatively reflect the rate of the reaction, there is a difference for the susceptibility of cleaving the O^2,2'-anhydro linkage of 1a by the nucleophiles. The rate of this reaction would depend on the pKa value of the thiols(e.g. pKa values for thiophenol, p-chlorothiophenol, and p-toluenethiol are 8.4, 9.3, and 7.8, respectively[4]), therefore protonation at the base moiety of 1a would be one of the most important factors in this reaction. Indeed, alkyl mercaptans and even benzyl mercaptan did not have the ability to cleave the O^2,2'-anhydro linkage of 1a.

GENERAL PROCEDURE

2'-Deoxy-2'-Arylthiouridines---To a suspension of O^2,2'-cyclouridine(1a) (678 mg, 3 mmol) in dimethylformamide(15 ml) was added aromatic thiols(1.5-2 equimol). The mixture was heated under reflux for an appropriate period(see Table 1) with stirring. The cooled solution was evaporated to dryness in vacuo. The resulting oil or solid was crystallized from EtOH. In the case of 6e and 6f, the residue was purified by silica gel column chromatography to remove unreacted 1a. The physical data are given in Table 1. ^{1}H NMR parameters are listed in Table 2.

Analysis Data---6a; Calcd for: C, 53.56; H, 4.80; N, 8.33. Found: C,53.51; H, 4.87; N, 8.53. 6b; Calcd for: C, 52.45; H, 4.95; N, 7.64. Found: C, 52.38; H, 5.06; N, 7.70. 6c; Calcd for: C, 48.67; H, 4.08; N, 7.57. Found: C,48.99; H, 4.06; N, 7.56. 6d; Calcd for: C, 54.85; H, 5.18; N, 7.99. Found: C, 54.93; H, 5.19; N, 7.82. 6e; Calcd for: C, 54.85; H, 5.18; N, 7.99. Found: C, 55.03; H, 5.19; N, 7.96. 6f; Calcd for: C, 53.47; H, 5.33; N, 7.79. Found: C, 53.35; H, 5.28; N, 7.90. 6g; Calcd for: C, 59.06; H, 4.69; N, 7.25. Found: C, 59.17; H, 4.63; N, 7.32.

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