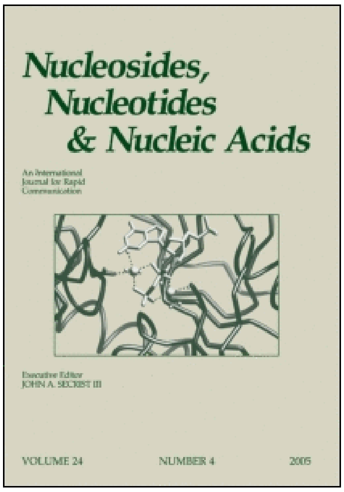

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Synthesis of 5-Arylthiouridines via Electrophilic Substitution of 5-Bromouridines with Diaryl Disulfides

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SYNTHESIS OF 5-ARYLTHIOURIDINES VIA ELECTROPHILIC SUBSTITUTION OF 5-BROMOURIDINES WITH DIARYL DISULFIDES

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ABSTRACT: Novel synthetic method of 5-arylthiouridine derivatives is described. Treatment of 5-bromo-2',3'-*O*-isopropylideneuridine (**1a**) with diaryl disulfides in the presence of sodium hydride at ambient temperature gave the 5-arylthiouridines (**2**) in moderate yields. The present method is devised by virtue of a combination of efficient participation of the 5'-hydroxy group onto the uracil ring and the electrophilic nature of diaryl disulfide, which was applied to the synthesis of 5-arylthio-1-β-D-arabinofuranosyluracils (**8**).

The development of new methods for the synthesis of 5-substituted uridine derivatives represents an important area of drug design for biologically active antimetabolites.[1] For this purpose, the reactions of 5-bromouridines with various nucleophiles such as sulfur nucleophiles,[2] amines,[3] cyanide ion,[4] etc.[5] have been extensively investigated. In order to synthesize 5-(substituted thio)uridine derivatives, thiol compounds have been employed as a nucleophile in the reaction with 5-bromouridines. However, the drawback to this method is that a debrominated product is formed as a by-product together with the expected 5-(substituted thio)uridine[2]. In the course of our study on the bromination of 2',3'-*O*-isopropylideneuridine, we found an electrophilic addition to the 5,6-double bond accompanied with neighboring-group participation of the 5'-hydroxy group.[6] This finding led to development of a novel method for the synthesis of 5-

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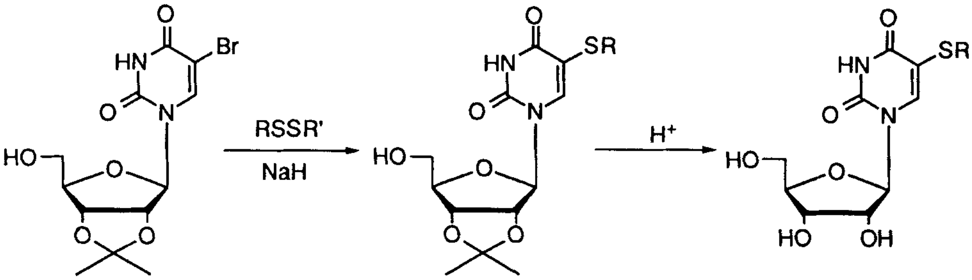
This paper is dedicated to the late Professor Tsujiaki Hata who made great contributions to nucleic acids chemistry.

arylthiouridine derivatives by the reaction of 5-bromo-2',3'-*O*-isopropylideneuridine (**1a**) with diaryl disulfides.[7] In this paper further examples of the synthesis of 5-arylthiouridines and the scope and limitation of this methodology are described.

In our initial study, treatment of the uridine (**1a**) (1.0 mmol) with diphenyl disulfide (1.2 mmol) in the presence of sodium hydride (2.0 mmol) in dry dimethylformamide (DMF) at 90 °C afforded the corresponding 5-phenylthiouridine (**2a**) in 78% yield. The structure of **2a** was confirmed by spectral comparison with an authentic sample which was alternatively prepared by the reaction of **1a** with sodium phenylthiolate.[8] To establish the generality of this electrophilic substitution reaction, the uridine (**1a**) was subjected to an analogous reaction with various disulfides in DMF. The results are summarized in TABLE 1. The substitution proceeded in good yields in the case of electron-deficient disulfides such as bis(*p*-nitrophenyl) disulfide and 4,4'-dipyridyl disulfide. In contrast to the case of the diaryl disulfide, the reaction with dialkyl disulfides, e.g., diethyl disulfide, gave 5-ethylthiouridine (**2f**) in only 18 % yield. Ultimately, the yield of **2f** was improved by the use of ethyl 2,4-dinitrophenyl disulfide which exhibits higher electrophilic property. Deprotection of the 5-(substituted thio)uridines (**2**) prepared here was performed with trifluoroacetic acid (TFA) in water to give 5-(substituted thio)uridines **3** (TABLE 1).

The present substitution reaction was successfully applied to the corresponding diphenyl diselenide. When the 5-bromouridine (**1a**) was allowed to react with diphenyl diselenide in the presence of sodium hydride at 90 °C, the 5-phenylselenouridine **4** was obtained in 43% yield together with O^6,5'-cyclo-2',3'-*O*-isopropylidene-5-phenylselenouridine (**5**, 2% yield).

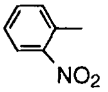
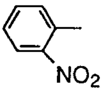
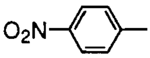
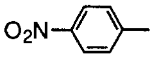
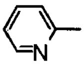
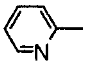
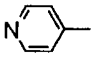
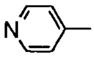
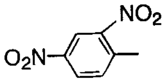
The reaction of 5-bromouridine (**1b**) and 5-bromo-2'-deoxyuridine (**1c**), which have no isopropylidene protecting group in the sugar moiety, with diphenyl disulfide under similar conditions[9] gave only a poor yield of the expected 5-phenylthiouridine (**3a** and **6**), respectively, and a large amount of the starting materials was recovered (see TABLE 2). The reaction of 5-bromo-1-methyluracil (**1d**), possessing no 5'-hydroxyl group with diphenyl disulfide did not afford the corresponding 5-phenylthio derivative at all. On the other hand, the use of 5-bromo-1-β-D-arabinofuranosyluracil (**1e**) facilitated the substitution reaction and the yield of 5-arylthiouracil (**8a-c**) was enhanced (26-35%) in spite of its shorter reaction time (30 min-25 h). When the reaction of **1a** with diphenyl disulfide was carried out in the absence of the base (sodium hydride), the starting material was completely recovered.

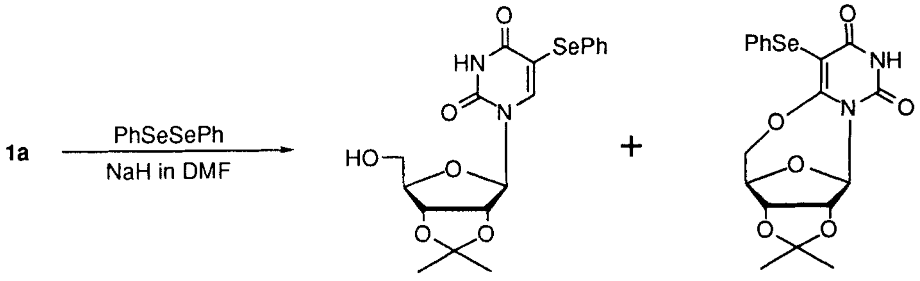


1a **2** **3**

SCHEME 1

TABLE 1. Formation of 5-(Substituted thio)uridines (2 and 3)

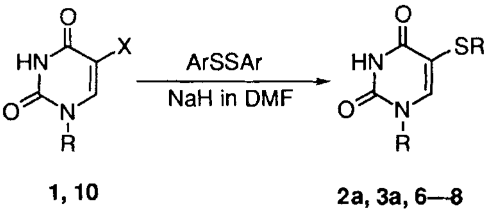
R	R'	Time (h)	Yield (%)			
			2		3	
Ph	Ph	48	**2a**	78	**3a**	64
		1.2	**2b**	55	**3b**	84
		1.3	**2c**	93	**3c**	87
		72	**2d**	41	**3d**	67
		3	**2e**	80	**3e**	69
Et	Et	96	**2f**	18	**3f**	46
Et		24	**2f**	38	—	



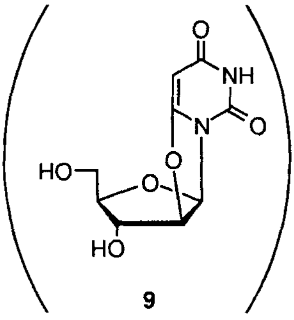
4 **5**

SCHEME 2

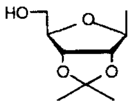
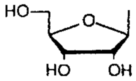
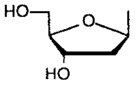
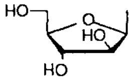
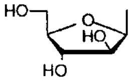
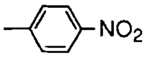
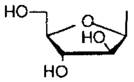
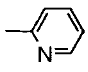
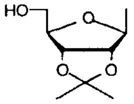
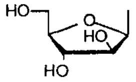
TABLE 2. Effects of N(1)-Substituent on the electrophilic substitution reaction



1, 10 **2a, 3a, 6—8**



9

Compd	R	X	Ar	Time	Yield (%)
1a		Br	Ph	48 h	**2a** 78
1b		Br	Ph	10 days	**3a** 3
1c		I	Ph	4 days	**6** 6
1d	Me	Br	Ph	24 h	**7** 0
1e		Br	Ph	1 h	**8a** 26 + **9**[10] 37
1e		Br		30 min	**8b** 39
1e		Br		25 h	**8c** 35
10a		H	Ph	2 weeks	**2a** 18
10b		H	Ph	25 h	**8a** 49

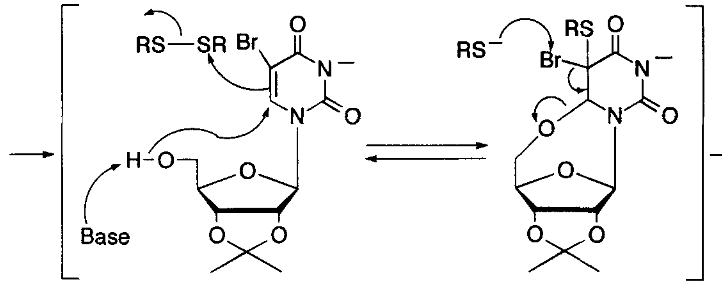
The above results indicate that the hydroxy group at the 5'-position or the 2'-β-hydroxy group plays an important role in the electrophilic substitution reaction. The formation of *O*^{6},2'-cyclo-1-β-D-arabinofuranosyluracil (**9**) together with **8a** suggests a reaction mechanism involving neighboring-group participation, that is, an attack of 5'- or 2'-β-hydroxy group on the 6-position of the uracil ring.[6, 10] A plausible reaction sequence for the formation of 2',3'-*O*-isopropylidene-5-thiouridines (**2**) is outlined in Scheme 3. An electrophilic addition of the disulfide to the 5-position of **1a** could be induced by the nucleophilic attack of the 5'-oxy anion on the 6-position of the uracil ring to give the 5,6-dihydro-adduct and a thiolate ion. The subsequent β-elimination promoted by the abstraction of the bromonium (Br^+) ion by the thiolate ion (by E2 Hal mechanism[11]) could produce 5-(substituted thio)uridines (**2**).[2]

As can be seen in TABLE 2, when 5-halogene-unsubstituted uracil derivatives such as 2',3'-*O*-isopropylideneuridine (**10a**) and 1-β-D-arabinofuranosyluracil (**10b**) were allowed to react with diphenyl disulfide, a similar type of electrophilic substitution proceeded to give the corresponding 5-phenylthiouracils (**2a** and **8a**). The reaction sequence for these electrophilic substitutions is shown representatively with the formation of **8a** in Scheme 4. Although Lee and Kim recently reported[12] the Mn (III)-mediated phenylselenenylation at the C-5 position of uracil derivatives, our phenylsulphenylation mechanism of **10a** and **10b** would be apparently distinct from theirs.

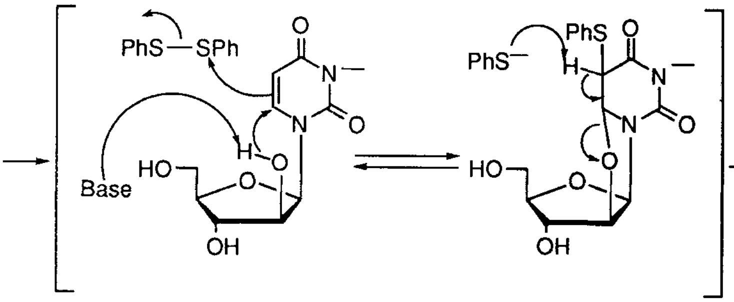
While the 5-(substituted thio)uracil derivatives (**3a-f**, **6** and **8a-c**) thus synthesized were evaluated for their antiviral activities against herpes simplex virus (HSV), adenovirus, vesicular stomatitis virus (VSV) and influenza A virus, these compounds uniformly indicated no antiviral activities except for only **3a** which exhibited weak anti-VSV activity.

EXPERIMENTAL

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. All column chromatography was carried out with silica gel (Wakogel, C-300). All reactions were monitored by thin layer chromatography (TLC) performed on glass-backed silica gel 60 F254, 0.2 mm plates (MERCK), and compounds were visualized under UV light (254 nm). Melting points were determined on a Yanagimoto micro hot-stage apparatus and are uncorrected. ^1H NMR spectra were determined with a JEOL GX-270 or Hitachi Perkin-Elmer R-20B spectrometer using sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) in DMSO-d_6 as an internal standard.

1a

2

SCHEME 3

10b

8a

SCHEME 4

Coupling constants (*J*) are reported in hertz (Hz). Mass spectra (MS) were obtained in a JEOL JMS-D 300 machine operating at 70 eV. Microanalyses were carried out at the Microanalytical Laboratory of our university.

General Procedure for the Preparation of 2',3'-*O*-Isopropylidene-5-(substituted thio)uridine Derivatives (2a-f) Starting from 1a. A mixture of 5-bromo-2',3'-*O*-isopropylideneuridine (**1a**) (1 equiv), a disulfide (1.2 equiv) and sodium hydride (2 equiv) in dry DMF (5 mL/mmol) was heated at 90 °C for an appropriate time (see TABLE 1). DMF was removed *in vacuo,* and the residue was purified by silica gel column chromatography with an appropriate solvent (see below) as eluent to give **2a-f**.

2',3'-*O*-Isopropylidene-5-phenylthiouridine (2a). The residue was chromatographed using $CHCl_3$/MeOH = 40/1 as eluent and then recrystallized from EtOH, 55%, mp 172 °C; Uv (EtOH) λ_{max} 334 nm (sh, ε = 1.08 x 10^4), 304 nm (sh, ε = 0.54 x

10^4), 246 nm (ε = 1.51 x 10^4); MS (EI^+) *m/z* 392 (M^+); ^1H NMR δ 1.31 and 1.52 (each s, each 3H, CH_3), 3.52-3.68 (m, 2H, H-5'), 4.15 (d, 1H, *J* = 3.4 Hz, H-4'), 4.78 (dd, 1H, *J* = 3.4 and 6.2 Hz, H-3'), 5.03 (dd, 1H, *J* = 2.5 and 6.2 Hz, H-2'), 5.18 (t, 1H, *J* = 5.1 Hz, OH), 5.89 (d, 1H, *J* = 2.5 Hz, H-1'), 7.15-7.35 (m, 5H, SPh), 8.43 (s, 1H, H-6), 11.78 (br, 1H, HN^3). Anal. Calcd for $C_{18}H_{20}N_2O_6S$: C, 55.09; H. 5.14; N, 7.14. Found: C, 54.97; H, 5.22; N, 7.16.

2',3'-*O*-Isopropylidene-5-(2-nitrophenylthio)uridine (2b). The residue was chromatographed using $CHCl_3$/MeOH = 30/1 as eluent and then recrystallized from EtOH, 55%, mp 231—233 °C; Uv (EtOH) λ_{max} 360 nm (ε = 0.52 x 10^4), 271 nm (ε = 1.36 x 10^4), 242 nm (ε = 1.89 x 10^4); MS (EI^+) *m/z* 437 (M^+); ^1H NMR δ 1.32 and 1.52 (each s, each 3H, CH_3), 3.45-3.79 (m, 2H, H-5'), 4.08-4.51 (m, 1H, H-4'), 4.80 (dd, 1H, *J* = 3.0 and 6.5 Hz, H-3'), 5.10 (dd, 1H, *J* = 2.2 and 6.5 Hz, H-2'), 5.22 (t, 1H, *J* = 2.1 Hz, OH), 5.96 (d, 1H, *J* = 2.2 Hz, H-1'), 7.90-7.31 (m, 3H, H-4, H-5 and H-6 of benzene ring), 8.22-8.46 (m, 1H, H-3 of benzene ring), 8.59 (s, 1H, H-6), 11.81 (br, 1H, HN^3). Anal. Calcd for $C_{18}H_{19}N_3O_8S \cdot 1/10H_2O$: C, 49.22; H. 4.40; N, 9.57. Found: C, 48.95; H, 4.39; N, 9.50.

2',3'-*O*-Isopropylidene-5-(4-nitrophenylthio)uridine (2c). The residue was chromatographed using benzene/EtOAc = 2/1 as eluent and then recrystallized from EtOH, 93%, mp 130 °C; Uv (EtOH) λ_{max} 331 nm (ε = 1.55 x 10^4), 277 nm (ε = 0.87 x 10^4), 265 nm (ε = 0.91 x 10^4); MS (EI^+) *m/z* 437 (M^+); ^1H NMR δ 1.31 and 1.51 (each s, each 3H, CH_3), 3.46-3.75 (m, 2H, H-5'), 3.92-4.35 (m, 1H, H-4'), 4.70-5.38 (m, 3H, H-2', H-3' and OH), 5.93 (d, 1H, *J* = 1.8 Hz, H-1'), 5.22 (t, 1H, *J* = 2.1 Hz, OH), 7.49 (d, 2H, *J* = 8.7 Hz, H-2 and H-6 of benzene ring), 8.18 (d, 2H, *J* = 8.7 Hz, H-3 and H-5 of benzene ring), 8.58 (s, 1H, H-6), 11.83 (br, 1H, HN^3). Anal. Calcd for $C_{18}H_{19}N_3O_8S$: C, 49.43; H. 4.38; N, 9.61. Found: C, 49.14; H, 4.37; N, 9.45.

2',3'-*O*-Isopropylidene-5-(2-pyridylthio)uridine (2d). The residue was chromatographed using $CHCl_3$/MeOH = 50/1 as eluent and then recrystallized from EtOH, 41%, mp 193-195 °C; Uv (EtOH) λ_{max} 283 nm (ε =1.10 x 10^4), 240 nm (ε = 1.26 x 10^4); MS (EI^+) *m/z* 393 (M^+); ^1H NMR δ 1.31 and 1.51 (each s, each 3H, CH_3), 3.48-3.78 (m, 2H, H-5'), 3.98-4.31 (dt, 2H, *J* = 1.2 and 6.8 Hz, H-4 and H-6 of pyridine ring), 4.79-5.28 (m, 3H, H-2', H-3' and OH), 5.94 (d, 1H, *J* = 2.2, H-1'), 7.18 (t, 1H, *J* = 2.1 Hz, OH), 5.96 (d, 1H, *J* = 2.2 Hz, H-1'), 7.90-7.31 (m, 3H, H-4, H-5 and H-6 of benzene ring), 8.32-8.45 (m, 1H, H-3 of pyridine ring), 8.48 (s, 1H, H-6), 11.73 (br, 1H, HN^3).

Anal. Calcd for $C_{17}H_{19}N_3O_6S \cdot 1/2H_2O$: C, 50.74; H. 5.01; N, 10.44. Found: C, 50.89; H, 4.88; N, 10.41.

2',3'-*O*-Isopropylidene-5-(4-pyridylthio)uridine (2e). The residue was chromatographed using $CHCl_3$/MeOH = 30/1 as eluent and then recrystallized from EtOH, 80%, mp 237—239 °C; Uv (EtOH) λ_{max} 318 nm (sh, ε = 1.02 x 10^4), 258 nm (ε = 1.40 x 10^4); MS (EI^+) *m/z* 393 (M^+); ^1H NMR δ 1.30 and 1.50 (each s, each 3H, CH_3), 3.48-3.83 (m, 2H, H-5'), 4.10-4.45 (m, 1H, H-4'), 4.70-5.38 (m, 3H, H-2',H-3' and OH), 5.94 (d, 1H, *J* = 1.9 Hz, H-1'),7.25 (dd, 2H, *J* = 1.2 and 6.4 Hz, H-2 and H-6 of pyridine ring), 8.42 (dd, 2H, *J* = 1.2 and 6.4 Hz, H-3 and H-5 of pyridine ring), 8.55 (s, 1H, H-6), 11.81 (br, 1H, HN^3). Anal. Calcd for $C_{17}H_{19}N_3O_6S \cdot 3/4H_2O$: C, 50.18; H. 5.08; N, 10.33. Found: C, 50.41; H, 5.04; N, 10.09.

5-Ethylthio-2',3'-*O*-isopropylideneuridine (2f). The residue was chromatographed using $CHCl_3$/MeOH = 30/1 as eluent and then recrystallized from EtOH, 80%, mp 172-173 °C; Uv (EtOH) λ_{max} 290 nm (sh, ε = 0.43 x 10^4), 245 nm (ε = 0.51 x 10^4), 232 nm (ε = 0.53 x 10^4 L/mol cm); MS (EI^+) *m/z* 344 (M^+); ^1H NMR δ 1.16 (s, 3H, CH_3), 1.31 and 1.51 (each s, each 3H, CH_3), 3.48-3.83 (m, 2H, H-5'), 4.10-4.45 (m, 1H, H-4'), 4.70-5.38 (m, 3H, H-2',H-3' and OH), 5.94 (d, 1H, *J* = 1.9 Hz, H-1'),7.25 (dd, 2H, *J* = 1.2 and 6.4 Hz, H-2 and H-6 of pyridine ring), 8.42 (dd, 2H, *J* = 1.2 and 6.4 Hz, H-3 and H-5 of pyridine ring), 8.55 (s, 1H, H-6), 11.81 (br, 1H, HN^3). Anal. Calcd for $C_{17}H_{19}N_3O_6S \cdot 3/4H_2O$: C, 50.18; H. 5.08; N, 10.33. Found: C, 50.41; H, 5.04; N, 10.09.

General Procedure for the Preparation of 5-(Substituted thio)uridine (3a-f). A mixture of 2',3'-*O*-isopropylidene-5-(substituted thio)uridine (**2a-f**) (1 equiv), trifluoroacetic acid (10-20 mL/mmol) and water (10-20 mL/mmol) was stirred at room temperature for an appropriate time (see below). Solvents were removed *in vacuo* and the residue was recrystallized from an appropriate solvent (see below) to give **3a-f**.

5-Phenylthiouridine (3a). The mixture was stirred for 30 min and recrystallized from EtOH, 64%, mp 189-192 °C; Uv (EtOH) λ_{max} 341 nm (sh, ε = 0.93 x 10^4), 308 nm (sh, ε = 0.46 x 10^4), 246 nm (ε = 1.13 x 10^4); MS (EI^+) *m/z* 352 (M^+); ^1H NMR δ 3.30-4.13 (m, 5H, H-2', H-3', H-4' and H-5'), 5.12 (m, 1H, OH), 5.23 (m, 1H, OH), 5.50 (d, 1H, *J* = 5.1 Hz, OH), 5.79 (d, 1H, *J* = 4.4 Hz, H-1'), 7.16-7.35 (m, 5H, S-Ph), 8.60 (s, 1H, H-6), 11.72 (br, 1H, HN^3). Anal. Calcd for $C_{15}H_{16}N_2O_6S \cdot 1/5H_2O$: C, 50.61; H. 4.64; N, 7.87. Found: C, 50.54; H, 4.63; N, 8.10.

5-(2-Nitrophenylthio)uridine (3b). The mixture was stirred for 3 h and recrystallized from water, 84%, mp 203-207 °C; Uv (EtOH) λ_{max} 360 nm ($\varepsilon = 0.51 \times 10^4$), 271 nm ($\varepsilon = 1.28 \times 10^4$), 241 nm ($\varepsilon = 1.78 \times 10^4$); MS (EI$^+$) *m/z* 397 (M$^+$); ^{1}H NMR δ 3.50-3.80 (m, 2H, H-5'), 3.81-4.29 (m, 3H, H-2', H-3' and H-4'), 4.98-5.41 (m, 2H, 2 x OH), 5.52 (br d, 1H, *J* = 4.4 Hz, OH), 5.86 (d, 1H, *J* = 2.9 Hz, H-1'), 7.29-7.80(m, 3H, H-4,H-5 and H-6 of benzene ring), 8.20-8.45 (m, 1H, H-3 of benzene ring), 8.78 (s, 1H, H-6), 11.75 (br, 1H, HN^3). Anal. Calcd for $C_{15}H_{15}N_3O_8S \cdot 1/2H_2O$: C, 44.34; H. 3.97; N, 10.34. Found: C, 44.55; H, 3.80; N, 10.25.

5-(4-Nitrophenylthio)uridine (3c). The mixture was stirred for 1 h and recrystallized from water, 87%, mp 247-278 °C; Uv (EtOH) λ_{max} 329 nm ($\varepsilon = 1.61 \times 10^4$), 279 nm ($\varepsilon = 0.92 \times 10^4$); MS (EI$^+$) *m/z* 397 (M$^+$); ^{1}H NMR δ 3.56-3.82 (m, 2H, H-5'), 3.82-4.32 (m, 3H, H-2', H-3' and H-4'), 4.97-5.65 (m, 3H, 3 x OH), 5.86 (d, 1H, *J* = 3.2 Hz, H-1'), 7.48 (d, 2H, *J* = 8.9 Hz, H-2 and H-6 of benzene ring), 8.21 (d, 2H, *J* = 8.9 Hz, H-3 and H-5 of benzene ring), 8.78 (s, 1H, H-6), 11.79 (br, 1H, HN^3). Anal. Calcd for $C_{15}H_{15}N_3O_8S$: C, 45.34; H. 3.81; N, 10.57. Found: C, 45.48; H, 3.80; N, 10.61.

5-(2-Pyridylthio)uridine (3d). The mixture was stirred for 30 min and recrystallized from EtOH, 67%, mp 213-215 °C; Uv (EtOH) λ_{max} 283 nm ($\varepsilon = 1.16 \times 10^4$), 240 nm ($\varepsilon = 1.26 \times 10^4$); MS (EI$^+$) *m/z* 353 (M$^+$); ^{1}H NMR δ 3.52-3.72 (m, 2H, H-5'), 3.87-4.26 (m, 3H, H-2', H-3' and H-4'), 5.32 (br, 3H, 3 x OH), 5.81 (d, 1H, *J* = 4.4 Hz, H-1'), 7.12-7.26 (m, 2H, H-4 and H-6 of pyridine ring), 7.64-7.73 (m, 1H, H-5 of pyridine ring), 8.40 (d, 1H, *J* = 4.8 Hz, H-3 of pyridine ring), 8.62 (s, 1H, H-6), 11.76 (br, 1H, HN^3). Anal. Calcd for $C_{14}H_{15}N_3O_6S \cdot CF_3COOH$: C, 41.12; H. 3.45; N, 8.99. Found: C, 41.46; H, 3.70; N, 8.91.

5-(4-Pyridylthio)uridine (3e). The mixture was stirred for 30 min and recrystallized from EtOH, 69%, mp 237-240 °C; Uv (EtOH) λ_{max} 283 nm (sh, $\varepsilon = 1.11 \times 10^4$), 260 nm ($\varepsilon = 1.43 \times 10^4$); MS (EI$^+$) *m/z* 353 (M$^+$); ^{1}H NMR δ 3.70 (br, 2H, H-5'), 3.82-4.20 (m, 3H, H-2', H-3' and H-4'), 5.84 (d, 1H, *J* = 2.2 Hz, H-1'), 7.20-7.99 (br, 3H, 3 x OH), 7.79 (d, 2H, *J* = 6.5 Hz, H-2 and H-6 of pyridine ring), 8.68 (d, 2H, *J* = 6.5 Hz, H-3 and H-5 of pyridine ring), 8.86 (s, 1H, H-6), 11.89 (br, 1H, HN^3). Anal. Calcd for $C_{14}H_{15}N_3O_6S \cdot CF_3COOH$: C, 41.12; H. 3.45; N, 8.99. Found: C, 40.85; H, 3.44; N, 9.03.

5-Ethylthiouridine (3f). The mixture was stirred for 30 min and recrystallized from EtOH, 46%, mp 186-187 °C; Uv (EtOH) λ_{max} 288 nm ($\varepsilon = 0.55 \times 10^4$), 240 nm ($\varepsilon$ =

0.59×10^4); MS (EI$^+$) *m/z* 304 (M$^+$); ^{1}H NMR δ 1.16 (t, 3H, *J* = 7.3 Hz, CH_3), 2.71 (q, 2H, *J* = 7.3 Hz, CH_2), 3.59 (d, 1H, *J* = 2.1 Hz, H-5'), 3.69 (d, 1H, *J* = 2.1 Hz, H-5'), 3.90 (d, 1H, *J* = 3.7 Hz, H-4'), 4.01 (br, 2H, H-3'), 4.08 (br, 1H, H-2'), 5.10 (br, 1H, OH), 5.22 (br, 1H, OH), 5.41 (br, 1H, OH), 5.80 (d, 1H, *J* = 4.8 Hz, H-1'), 8.16 (s, 1H, H-6), 11.58 (br, 1H, HN^3). Anal. Calcd for $C_{11}H_{16}N_2O_6S$: C, 43.42; H. 5.30; N, 9.21. Found: C, 43.23; H, 5.17; N, 9.21.

2',3'-*O*-Isopropylidene-5-phenylselenouridine (4) and *O*^{6},5'-Cyclo-2',3'-*O*-isopropylidene-5-phenylselenouridine (5). A mixture of **1a** (726 mg, 2.0 mmol), diphenyl diselenide (750 mg, 2.4 mmol) and 60% sodium hydride (160 mg, 4.0 mmol) in dry DMF (10 mL) was heated at 90 °C for 23 h. DMF was removed *in vacuo,* and the residue was purified by silica gel column chromatography (benzene/AcOEt = 2/1) to give **4** (380 mg, 43%) and **5** (16 mg, 2%). **4**; foam; Uv (EtOH) λ_{max} 308 nm (sh, $\varepsilon = 0.08 \times 10^4$), 348 nm ($\varepsilon = 0.26 \times 10^4$); MS (EI$^+$) m/z 440 (M$^+$); ^{1}H NMR (DMSO-*d*$_6$) δ 1.32 and 1,51 (each s, each 3H, CH_3), 3.40-3.74 (m, 2H, H-5'), 3.98-4.32 (m, 1H, H-4'), 4.06-5.33 (m, 3H, H-2', H-3' and OH), 5.92 (d, 1H, *J* = 2.0 Hz, H-1'), 7.12-7.65 (m, 5H, S-Ph), 8.36 (s, 1H, H-6), 11.67 (br, 1H, HN^3). *Anal.* Calcd for $C_{18}H_{20}N_2O_6Se$: C, 49.21 H, 4.59; N, 6.38. Found: C, 49.20; H, 4.77; N, 6.17. **5**; mp 226 °C; Uv (EtOH) λ_{max} 304 nm ($\varepsilon = 0.29 \times 10^4$), 253 nm ($\varepsilon = 1.21 \times 10^4$); MS (EI$^+$) m/z 438 (M$^+$); ^{1}H NMR (DMSO-*d*$_6$) δ 1.30 and 1.45 (each s, each 3H, CH_3), 3.96 (d, 1H, *J* = 12.2 Hz, H-5'), 4.61 (d, 1H, *J* = 12.2 Hz, H-5'), 4.63 (s, 1H, H-4'), 4.99 (br s, 2H, H-2' and H-3'), 6.34 (s, 1H, H-1'), 7.14-7.46 (m, 5H, S-Ph), 11.74 (br, 1H, HN^3). *Anal.* Calcd for $C_{18}H_{18}N_2O_6Se$: C, 49.44 H, 4.15; N, 6.41. Found: C, 49.23; H, 4.18; N, 6.37.

Reaction of 1-Substituted 5-Halogenouracils (1b, c, d, e) with Diaryl Disufides: General Procedure (3a, 6, 8a-c). A mixture of a 5-halogenouracil (**1b, c, d, e**) (1 equiv), a diaryl disufide (2 equiv) and sodium hydride (2 equiv) in dry DMF (5 mL/mmol) was stirred at 90 °C for an appropriate time (see TABLE 2). DMF was removed *in vacuo,* and the residue was purified by silica gel column chromatography with an appropriate solvent (see below) as eluent to give 1-substituted 5-arylthiouracil derivatives (**3a, 6, 8a-c**).

5-Phenylthiouridine (3a). The residue was chromatographed using $CHCl_3$/MeOH = 5/1 as eluent and then recrystallized from EtOH, 3% (84% recovery), which was identical with the product obtained from the reaction of compound **2a** with TFA.

2'-Deoxy-5-phenylthiouridine (6). The residue was chromatographed using $CHCl_3$/MeOH = 20/1 as eluent and then recrystallized from EtOH, 6% (18% recovery), mp 188-190 °C; Uv (EtOH) λ_{max} 340 nm (sh, $\varepsilon = 0.74 \times 10^4$ L/mol cm), 308 nm (sh, $\varepsilon = 0.36 \times 10^4$), 246 nm ($\varepsilon = 0.92 \times 10^4$); MS (EI$^+$) *m/z* 336 (M$^+$); ^{1}H NMR δ 3.40-3.68 (m, 3H, H-4' and H-5'), 3.83 (d, 1H, *J* = 3.3 Hz, H-3'), 4.22-4.30 (m, 2H, H-2'), 5.13 (t, 1H, *J* = 4.9 Hz, OH), 5.29 (d, 1H, *J* = 4.0 Hz, OH), 6.16 (t, 1H, *J* = 6.4 Hz, H-1'), 7.19-7.37 (m, 5H, SPh), 8.48 (s, 1H, H-6), 11.70 (br, 1H, HN^3). Anal. Calcd for $C_{15}H_{16}N_2O_5S$: C, 53.56; H. 4.79; N, 8.33. Found: C, 53.65; H, 4.86; N, 8.30.

1-β-D-Arabinofuranosyl-5-phenylthiouracil (8a). The residue was chromatographed using $CHCl_3$/MeOH = 30/1 as eluent and then recrystallized from water, 26% [together with 37% of O^6,2'-cyclo-1-β-D-arabinofuranosyluracil (**9**)[10b]], mp 236-238 °C; Uv (EtOH) λ_{max} 341 nm (sh, $\varepsilon = 0.78 \times 10^4$), 308 nm (sh, $\varepsilon = 0.39 \times 10^4$), 246 nm ($\varepsilon = 0.98 \times 10^4$); MS (EI$^+$) *m/z* 352 (M$^+$); ^{1}H NMR δ 3.57 (d, 1H, *J* = 5.9 Hz, H-5'), 3.61 (d, 1H, *J* = 5.9 Hz, H-5'), 3.78 (m, 1H, H-4'), 3.94 (m, 1H, H-3'), 4.06 (m, 1H, H-2'), 5.12 (t, 1H, *J* = 5.5 Hz, OH), 5.52 (d, 1H, *J* = 4.4 Hz, OH), 5.71 (d, 1H, *J* = 5.1 Hz, OH), 6.05 (d, 1H, *J* = 4.4 Hz, H-1'), 7.13-7.35 (m, 5H, SPh), 8.13 (s, 1H, H-6), 11.73 (br, 1H, HN^3). Anal. Calcd for $C_{15}H_{16}N_2O_6S$: C, 51.13; H. 4.58; N, 7.95. Found: C, 51.18; H, 4.60; N, 8.00.

1-β-D-Arabinofuranosyl-5-(4-nitrophenylthio)uracil (8b). The residue was chromatograph-ed using $CHCl_3$/AcOEt/MeOH = 15/15/1 as eluent, 39%, foam; Uv (MeOH) λ_{max} 328 nm and 270 nm; ^{1}H NMR δ 3.65 (m, 2H, *J* = 3.8 Hz, H-5'), 3.85 (m, 1H, *J* = 3.9 Hz, H-4'), 4.00 (m, 1H, *J* = 3.4 Hz, H-3'), 4.14 (m, 1H, *J* = 3.4 Hz, H-2'), 5.18 (t, 1H, *J* = 5.1 Hz, OH), 5.59 (d, 1H, *J* = 4.3 Hz, OH), 5.76 (d, 1H, *J* = 5.1 Hz, OH), 6.11 (d, 1H, *J* = 3.8 Hz, H-1'), 7.47 (d, 2H, *J* = 9.0 Hz, H-2 and H-6 of benzene ring), 8.20 (d, 2H, *J* = 9.0 Hz, H-3 and H-5 of benzene ring), 8.31 (s, 1H, H-6), 11.92 (br, 1H, HN^3); HREIMS m/z 397.0593 (M$^+$, calcd for $C_{15}H_{15}N_3O_8S$ 397.0597).

1-β-D-Arabinofuranosyl-5-(2-pyridylthio)uracil (8c). The residue was chromatographed using $CHCl_3$/AcOEt/MeOH = 30/1/1 as eluent, 35%, foam; Uv (MeOH) λ_{max} 282 nm and 241 nm; ^{1}H NMR δ 3.61 (m, 2H, H-5'), 3.75 (m, 1H, H-4'), 3.90 (m, 1H, H-3'), 4.01-4.04 (m, 1H, H-2'), 5.11 (br t, 1H, *J* = 5.1 Hz, OH), 5.50 (d, 1H, *J* = 4.3 Hz, OH), 5.66 (d, 1H, *J* = 5.2 Hz, OH), 6.02 (d, 1H, *J* = 4.3 Hz, H-1'), 7.13 (m, 2H, H-3 and H-5 of pyridine ring), 7.63 (t, 1H, *J* = 7.1 Hz, H-4 of pyridine ring), 8.15 (s, 1H, H-6), 8.36 (br d, 1H, *J* = 4.3 Hz, H-6 of pyridine ring), 11.78 (br, 1H, HN^3); HREIMS m/z 353.0669 (M$^+$, calcd for $C_{14}H_{15}N_3O_6S$ 353.0681).

Alternative Synthesis of 2',3'-*O*-Isopropylidene-5-phenylthiouridine (2a) Starting from 2',3'-*O*-Isopropylideneuridine (10a). A mixture of 2',3'-*O*-isopropylideneuridine (**10a**) (284 mg, 1.0 mmol), diphenyl disulfide (262 mg, 1.2 mmol) and 60% sodium hydride (80 mg, 2.0 mmol) in dry DMF (10 ml) was stirred at 90 °C for 2 weeks. The reaction mixture was evaporated under reduced pressure and the residue was chromatographed on a silica gel column ($CHCl_3$/MeOH = 30/1) to give **2a** (166 mg, 42%) and the starting compound **10a** (133 mg, 47%). The 5-phenylthiouridine (**2a**) was identical with the product obtained from the reaction of compound **1a** with diphenyl disulfide.

Alternative Synthesis of 1-β-D-Arabinofuranosyl-5-phenylthiouracil (8a) Starting from 1-β-D-Arabinofuranosyluracil (10b). A mixture of 1-β-D-arabinofuranosyluracil (**10b**) (244 mg, 1.0 mmol), diphenyl disulfide (1.31 g, 6.0 mmol) and 60% sodium hydride (80 mg, 2.0 mmol) in dry DMF (10 ml) was stirred at 120 °C for 25 h. The reaction mixture was evaporated under reduced pressure and the residue was chromatographed on a silica gel column ($CHCl_3$/MeOH = 20/1) to give **8a** (173 mg, 49%), which was identical with the product obtained from the reaction of compound **1e** with diphenyl disulfide.

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8. A debrominated product, 2',3'-*O*-isopropylideneuridine, was also isolated in 24% yield as a by-product as described previously.[2] On the other hand, the debrominated product was not detected by tlc analysis of the reaction mixture in the reaction of **1a** with diphenyl disulfide.
9. Although the reaction of **1b** which possesses more free hydroxyl groups than **1a** was also carried out in the presence of four equivalents of sodium hydride, the yield of **3a** was not improved.
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