

**ELECTROPHILIC IPSO-SUBSTITUTION OF 5-BROMOURIDINES WITH DIARYL
DISULFIDES. NOVEL SYNTHESIS OF 5-ARYLTHIOURIDINES**

Kosaku Hirota,* Tetsuo Tomishi, and Yoshifumi Maki

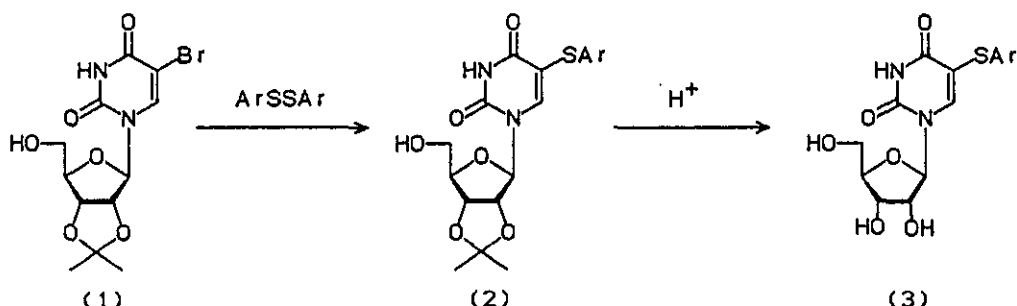
Gifu Pharmaceutical University, Mitahora-higashi, Gifu 502, Japan

Abstract - Reaction of 5-bromo-2',3'-O-isopropylideneuridine (1) with diaryl disulfides in the presence of base induced an electrophilic ipso-substitution to give 5-arylthiouridine derivatives (2).

Electrophilic substitution at the 5-position of uridines has been extensively investigated for the purpose of the synthesis of thymidine¹ and biologically active 5-substituted uridines.² On the other hand, although it is well known that 5-bromouridines are highly susceptible towards soft nucleophiles such as thiolate and cyanate ions,³ there have been only few examples of the reaction of 5-bromouridines with electrophiles in the literatures.⁴ In this paper we wish to describe that the reaction of 5-bromo-2',3'-O-isopropylideneuridine (1) with diaryl disulfides in the presence of base caused an electrophilic ipso-substitution⁵ to afford 5-arylthiouridines (2). The present reaction is devised by virtue of a combination of the efficient participation of 5'-hydroxy group on the uracil ring and the electrophilic nature of diaryl disulfides, which provides a novel synthetic method of 5-arylthiouridines.

To a mixture of the uridine (1) (1.0 mmol) and sodium hydride (2.0 mmol) in dry dimethylformamide was added diphenyl disulfide (1.2 mmol). The mixture was heated at 90 °C with stirring for 48h. After removal of the solvent, the residue was chromatographed over silica gel to give the 5-phenylthiouridine (2a)⁶ in 78% yield. The structure of 2a was confirmed by spectral comparison with an authentic sample prepared by the reaction of 1 with sodium phenylthiolate (vide infra). Analogous substitution reactions of 1 with various disulfides occurred with ease and the results are summarized in Table 1. In the case of employment of electron deficient disulfides such as bis(p-nitrophenyl) disulfide and 4,4'-dipyridyl

disulfide, the reaction proceeded in a comparatively high yield and short time (entry 3 and 5). Deprotection of 2a-e upon treatment with trifluoroacetic acid smoothly gave the corresponding 5-arylthiouridines (3a-e) (see Table 1).



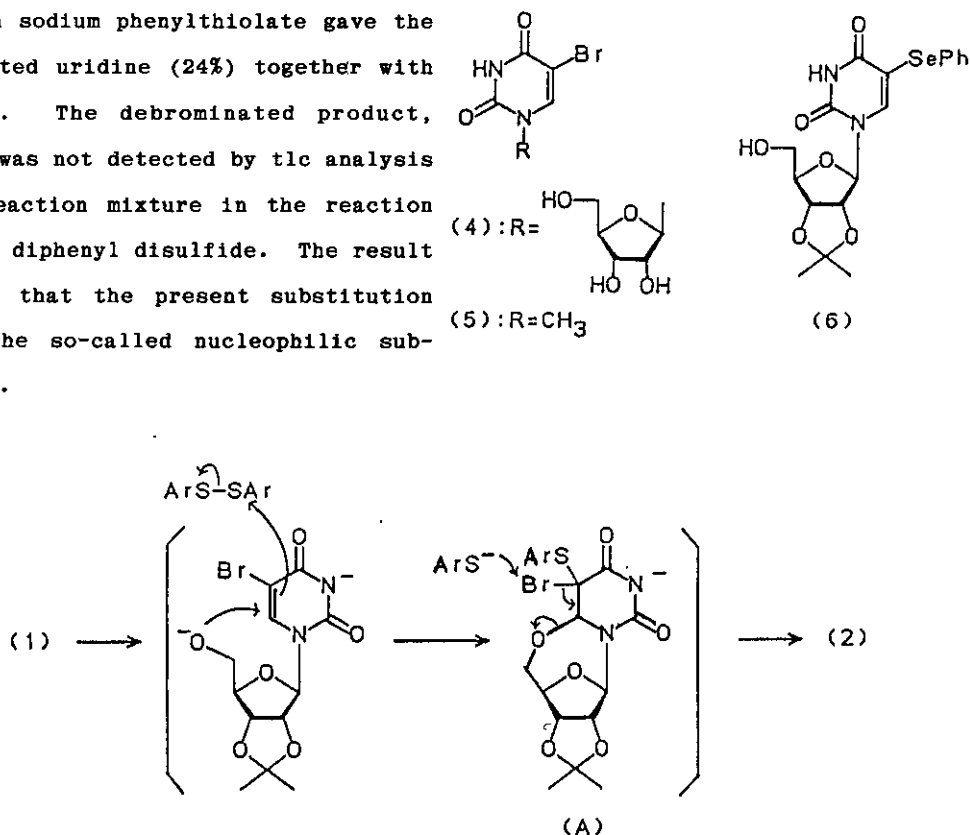
Scheme 1

Table 1. Formation of 5-Arylthiouridines (2 and 3)

Entry	ArSSAr Ar=	Reaction time (h)	(2) Yield(%)	(3) Yield(%)
1	Ph	48	(2a) 78	(3a) 64
2	<i>o</i> -NO ₂ C ₆ H ₄	1.2	(2b) 55	(3b) 84
3	<i>p</i> -NO ₂ C ₆ H ₄	1.3	(2c) 93	(3c) 87
4	2-pyridyl	72	(2d) 41	(3d) 67
5	4-pyridyl	3	(2e) 80	(3e) 69

When 2',3'-O-nonprotected 5-bromouridine (4) was allowed to react with diphenyl disulfide under the conditions similar to the case of 1, the expected 5-phenylthiouridine (3a) was obtained only in a poor yield (3%). In the reaction of 5-bromo-1-methyluracil (5) with diphenyl disulfide, the corresponding 5-phenylthio derivative was not obtained at all. These facts indicate clearly that the present reaction proceeds via an initial participation of the 5'-hydroxy group of the ribofuranosyl moiety. Generally, the reaction of 5-bromouridines with thiolate ions results in the concurrent formation of the 5-substituted product and the de-

brominated product.⁷ In fact, treatment of 1 with sodium phenylthiolate gave the debrominated uridine (24%) together with 2a (64%). The debrominated product, however, was not detected by tlc analysis of the reaction mixture in the reaction of 1 with diphenyl disulfide. The result indicates that the present substitution is not the so-called nucleophilic substitution.



Scheme 2

On the basis of above results a plausible reaction sequence for the formation of 5-arylthiouridines is outlined as depicted in Scheme 2. An electrophilic addition of the diaryl disulfide to the 5-position of 1 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 (A) and a thiolate ion. The subsequent β -elimination promoted by the abstraction of bromonium (Br^+) ion from (A) by the thiolate ion (by E2 Hal mechanism⁸) could produce 5-arylthiouridines (2).⁷

The present ipso-substitution reaction was successfully applied to diphenyl diselenide. When the 5-bromouridine (1) was treated with diphenyl diselenide in the presence of sodium hydride, the corresponding 5-phenylselenouridine (6) was obtained in 43% yield.

The electrophilic ipso-substitution reaction⁹ is of interest in connection with the crosslinking of 5-bromo-2'-deoxyuridine incorporated in DNA with proteins containing the S-S linkage.¹⁰

REFERENCES AND NOTES

1. S. S. Jones, C. B. Reese, and A. Ubasawa, Synthesis, 1982, 259; C. B. Reese and Y. S. Sanghvi, J. Chem. Soc., Chem. Commun., 1983, 877.
2. See, for example, B. R. Baker, T. J. Schwan, and D. V. Santi, J. Med. Chem., 1966, 9, 66; M. J. Robins and S. R. Naik, J. Am. Chem. Soc., 1971, 93, 5277; T. Nagamachi, J.-L. Fourrey, P. F. Torrence, J. A. Waters, and B. Witkop, J. Med. Chem., 1974, 17, 403; C. B. Reese and Y. S. Sanghvi, J. Chem. Soc., Chem. Commun., 1984, 62.
3. For a review see, T. K. Bradshaw and D. W. Hutchinson, Chem. Soc. Rev. 1977, 6, 43.
4. T. Maruyama, S. Kimura, Y. Sato, and M. Honjo, J. Org. Chem., 1983, 48, 2719; M. Marton-Meresz, J. Kuszmann, and I. Pelczer, Tetrahedron, 1983, 39, 275.
5. 2a: mp 172°C. ^1H NMR (CDCl_3) δ : 11.78 (1H, br, HN^3), 8.43 (1H, s, H-6), 7.35-7.15 (5H, m, S-Ph), 5.89 (1H, d, $J=2.5$ Hz, H-1'), 5.18 (1H, t, $J=5.1$ Hz, OH), 5.03 (1H, dd, $J=2.5$ and 6.2 Hz, H-2'), 4.78 (1H, dd, $J=3.4$ and 6.2 Hz, H-3'), 4.15 (1H, m, H-4'), 3.68-3.52 (2H, m, H-5'), 1.52 (3H, s, CH_3), 1.31 (3H, s, CH_3). $\text{UV}_{\lambda_{\text{max}}}^{\text{EtOH}}$ (ϵ): 304 (sh) (5400), 334 (sh) (11800), and 246 (15100). MS m/z : 392 (M^+). Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_6\text{S}$: C, 55.09; H, 5.14; N, 7.14. Found: C, 54.97; H, 5.22; N, 7.16. All new compounds described herein gave satisfactory microanalytical results and spectral data consistent with their structures.
6. K. Brederick and R. Schoner, Tetrahedron Lett., 1976, 4711; G. Angelini, G. Illuminati, A. Monaci, G. Sleiter, and M. Speranda, J. Am. Chem. Soc., 1980, 102, 1377.
7. E. G. Sander, 'Bioorganic Chemistry' vol. 2, ed. E. E. van Tamelen, Academic Press, New York, 1978, p 273.
8. Y. Wataya and D. V. Santi, J. Am. Chem. Soc., 1977, 99, 4534.
9. Employment of dialkyl disulfide such as diethyl disulfide as the protein model in stead of diaryl disulfide also resulted in the formation of the corresponding 5-alkylthiouridine although the yield was very low (5-ethylthio derivative, 6%).
10. T. M. Dietz, R. J. Trebra, B. J. Swanson, and T. H. Koch, J. Am. Chem. Soc., 1987, 109, 1793, and references cited therein.

Received, 17th August, 1987