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

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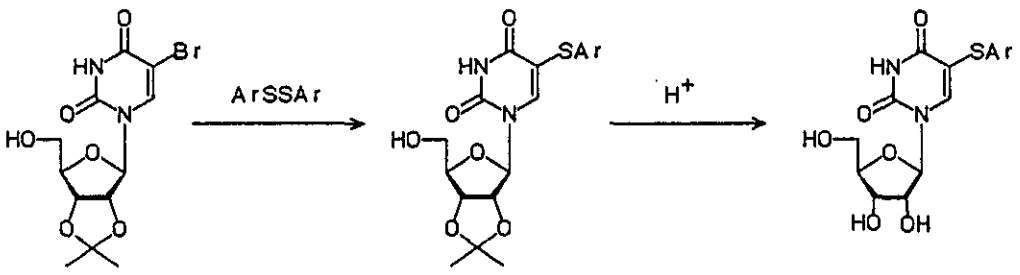
Abstract - Reaction of 5-bromo-2',3'-O-isopropylideneuridine (1) with diaryl disulfides in the presence of base induced an electrophilic ipso-substitution to give 5-arylthiouridine derivatives (2).

Electrophilic substitution at the 5-position of uridines has been extensively investigated for the purpose of the synthesis of thymidine[1] 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-substitution[5] 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).



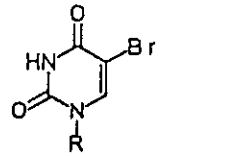
Scheme 1

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

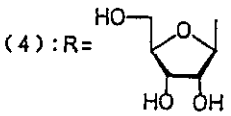
Entry	ArSSAr Ar=	Reaction time (h)	(2) Yield(%)	(3) Yield(%)
1	Ph	48	(**2a**) 78	(**3a**) 64
2	o-$NO_2C_6H_4$	1.2	(**2b**) 55	(**3b**) 84
3	p-$NO_2C_6H_4$	1.3	(**2c**) 93	(**3c**) 87
4	2-pyridyl	72	(**2d**) 41	(**3d**) 67
5	4-pyridyl	3	(**2e**) 80	(**3e**) 69

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-

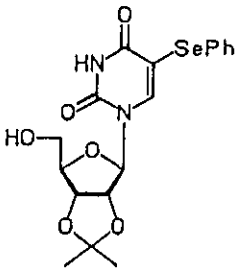
brominated product.[7] In fact, treatment of 1 with sodium phenylthiolate gave the debrominated uridine (24%) together with 2a (64%). The debrominated product, however, was not detected by tlc analysis of the reaction mixture in the reaction of 1 with diphenyl disulfide. The result indicates that the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



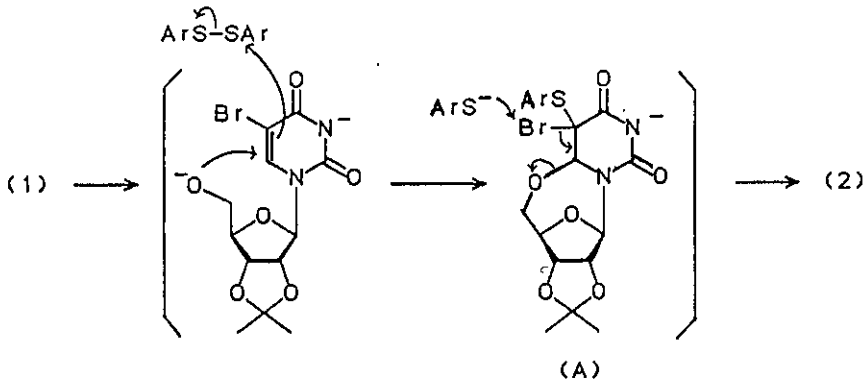
(4): R=



(5): R=CH_3



(6)



(A)

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 mechanism[8]) 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 reaction[9] 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

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5. **2a**: mp 172°C. ^{1}H 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). UV λ_{max}^{EtOH} (ε): 304 (sh) (5400), 334 (sh) (11800), and 246 (15100). MS m/z: 392 (M^+). 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. All new compounds described herein gave satisfactory microanalytical results and spectral data consistent with their structures.
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