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DIRECT REGIOSELECTIVE ARYLSULFENYLATION AND ARYLSELENENYLATION AT 5-POSITION OF URACILS MEDIATED BY SILVER REAGENTS

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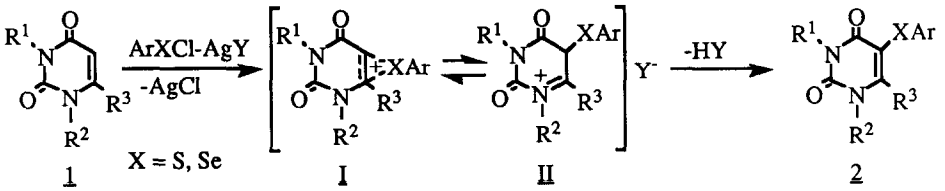
Summary : Electrophilic additions of phenylsulfenyl chloride or phenylselenenyl chloride to a carbon-carbon double bond of C-5,6 region of uracils in the presence of silver reagents such as Ag_2O, $AgBF_4$, or $AgOCOCF_3$ directly gave the corresponding 5-phenylsulfydryl- or 5-phenylselenenyl uracils in good yields.

A number of nucleosides incorporating a 5-substituted pyrimidine with a modified sugar attachment are currently undergoing evaluation as the antiviral agents.[1,2] In view of the pronounced biological activity, the 5-halogenated pyrimidines were exclusively used as intermediates for a variety of synthetic transformations of related compounds of biological interest, presumably because of the ease of substitution at this position.[3]

Since organic sulfur and selenium compounds have been known to be well utilized for the various transformations due to their some unique properties[4,5], in the new attempts for the functionalization of pyrimidine bases, the introduction of sulfur and selenium electrophiles at C-5 position of uracils was investigated.

During the course of a simple and direct method of introducing sulfur and selenium substitutents at C-5 position of pyrimidine nucleosides, it was found that electrophilic additions of phenylsulfenyl chloride or phenylselenenyl chloride to a carbon-carbon double bond of C-5,6 region of uracils in the presence of silver reagents such as Ag_2O, $AgBF_4$, or $AgOCOCF_3$ directly gave the corresponding 5-phenylsulfydryl- or 5-phenylselenenyl uracils in good yields in acetonitrile under mild conditions.



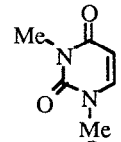
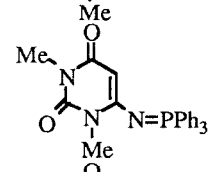
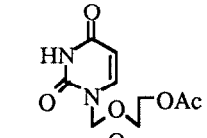
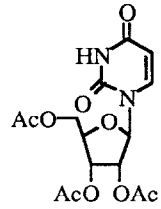
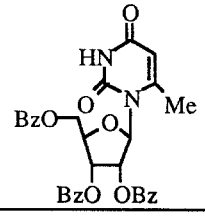
1 I II 2

R^1 = H, Me R^2 = Me, acyclic chain, ribose

R^3 = H, Me, N=PPh_3

In a typical procedure, to a solution of (2',3',5'-tri-O-acetyl)uridine (185 mg, 0.5 mmol) and silver trifluoroacetate ($AgOCOCF_3$, 166 mg, 0.75 mmol) in dry acetonitrile (4 ml) was added phenylselenenyl chloride (PhSeCl, 144 mg, 0.75 mmol) at ca. 15-20 °C. After stirring for 15 minutes, the resulting silver chloride (AgCl) was filtered off, the filtrate was concentrated, and then chromatographed on a short column of silica gel (Merck, column; 2.5 cm x 5 cm, eluent; CH_2Cl_2 : acetone (v/v) = 10 : 1) to afford the product of 5-phenylselenenyl-(2',3',5'-tri-O-acetyl)uridine (258 mg, 98 % yield, see the ref. 6). The results obtained are shown in Table 1.

Table 1. Arylsulfenylation and arylselenenylation of uracils at C-5 position

Run	Uracil	ArXCl[a]	AgY[a]	Time(h)	Temp(°C)	Yield[b](%)(2)
1		PhSCl	$AgBF_4$	0.5	0	89
2		PhSeCl	Ag_2O	2.5	15-20	73
3		PhSeCl	$AgBF_4$	1	15-20	97
4		PhSCl	$AgOCOCF_3$	0.5	0	96
5		PhSeCl	$AgBF_4$	1.5	15-20	89
6		PhSeCl	$AgOCOCF_3$	0.25	15-20	99
7		PhSCl	$AgBF_4$	2	0	47
8		PhSeCl	$AgOCOCF_3$	0.25	15-20	95
9		PhSCl	$AgBF_4$	3	0	45
10		PhSeCl	$AgBF_4$	2	15-20	88
11		PhSeCl	$AgOCOCF_3$	0.25	15-20	98
12		PhSCl	$AgBF_4$	2	0	82
13		PhSeCl	$AgBF_4$	2	15-20	91
14		PhSeCl	$AgOCOCF_3$	0.25	15-20	99

a) Molar ratio ; uracil : ArXCl : AgY = 1 : 1.5 : 1.5

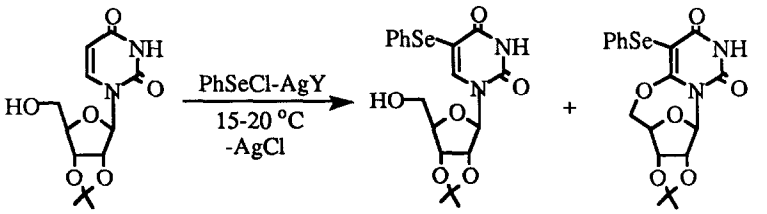
b) Isolated yields after chromatograpic purification

These direct arylsulfenylation and arylselenenylation occur regioselectively at the C-5 position of uracils. Any 6-substituted uracil products were not identified in all the cases.

In the absence of silver reagents such as $AgBF_4$ or $AgOCOCF_3$, the 5-substituted products were not also obtained. The starting material of uracil was recovered quantitatively and diphenyl disulfide or diphenyl diselenide was obtained after the usual aqueous work up. The essential feature of all these procedures is the use of non-nucleophilic and weak-basic counter ions[4] such as BF_4^- and $CF_3CO_2^-$. These electrophilic additions showed the moderate sensitivity to C-5,6-double bond containing electron-releasing groups such as iminotriphenylphosphorane- or methyl group accelerating the reactions[4,7], particularly in the arylsulfenylation reaction(Table 1, run 4-6, 12-14). These direct arylselenenylation reactions are also unusual because the common olefins containing arylselenenyl group have been obtained by the addition of arylselenenyl halide to the double bond, followed by the halide elimination with a basic treatment.[5]

In order to elucidate the reaction mechanism and the scope, the reaction of phenylselenenyl chloride with 2',3'-O-isopropylideneuridine(3) as a model compound containing 5'-hydroxyl group of the remote nucleophilic neighboring group on sugar[8] was performed in the presence or absence of silver reagents. It may be postulated that this direct arylselenenylation reaction proceeds *via* the formation of a seleniranium cation intermediate which would create a tremendous increase in electrophilic character at the C-6 position of uracil base.[9] The close proximity of the 5'-hydroxyl group could then allow cyclonucleoside formation(5)[10(b)] to occur. The results obtained are shown in Table 2.

Table 2. Reaction of 2',3'-O-isopropylidene uridine and PhSeCl



3 4 5

Run	Solvent	AgY[a]	Time (h)	Yield[b] (%)(4/5)
1	CH_2Cl_2	$AgBF_4$	1	20 (20/trace)
2	MeCN	none	2	trace
3	MeCN	Ag_2O	0.5	85 (85/3)
4	MeCN	$AgBF_4$	0.5	85 (85/2)
5	MeCN	$AgOCOCF_3$	0.25	98 (98/trace)

a) Molar ratio ; 3 : PhSeCl : AgY = 1 : 2 : 2

b) Isolated yields after chromatographic purification

The reaction mechanisms are considered as follows; (A) the eletrophilic addition of cationoid phenylselenium reagents of the type $PhSe^{+}Y^{-}$ proceeds *via* the relative unstable seleranium cation intermediate (I) and/or iminium-ion intermediate (II), which are subsequently followed by elimination of HY to afford the C-5 substituted uridine derivative (4)[10(a)] as a major product. It is reasonable to expect that the proton at C-5 would be more acidic than that at C-6 in intermediates (I, II) so that the elimination of HY occurs to give the C-5 substituted product exclusively[11]; (B) the relatively unstable cationic intermediates (I, II) which would also allow the nucleophilic attack of the proximate 5'-hydroxyl group to result in the cyclonucleoside (5) though it is a minor product.

Though the role of counter ions (Y^{-}) is not yet clear, it may be widely applicapable for the modifications of pyrimidine nucleosides.

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5. J. V. Comasseto, *J. Organomet. Chem.*, **253**, 131 (1983).
6. ^{1}H nmr ($CDCl_3$) δ 2.20 (t, 9H, three AcH's), 4.35 (br, 3H, H4',5'), 5.35 (m, 2H, H2',3'), 6.10 (d, $J_{1',2'}$ = 3 Hz, 1H, H1'), 7.20-7.60 (m, 5H, PhH's), 7.80 (s, 1H, H6); Mass (m/z) 526 (M^{+}).
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9. T. C. Thurber and L. B. Townsend, *J. Heterocycl. Chem.*, **9**, 629 (1972).
10. a) 4: IR (KBr) ν 3480, 3200, 1694, 1608, 1442, 1271, 1087 cm^{-1} ; ^{1}H nmr ($CDCl_3$) δ 1.48, 1.70 (d, 6H, two CH_3), 3.80 (m, 3H, H4',5'), 4.80 (br, 1H, C_5-OH), 5.00 (m, 2H, H2',3'), 5.76 (d, $J_{1',2'}$ = 2 Hz, 1H, H1'), 7.30-7.70 (m, 5H, PhH's), 7.76 (s, 1H, H6); Mass (m/z) 440 (M^{+}); (b) 5: ^{1}H nmr ($CDCl_3$) δ 1.34, 1.52 (d, 6H, two CH_3), 3.65, 4.35 (dd, $J_{4',5'}$ = 12 Hz, 2H, H5'), 4.52 (s, 1H, H4'), 4.85 (m, 2H, H2',3'), 6.57 (s, 1H, H1'), 7.10-7.50 (m, 5H, PhH's), 9.05 (br, 1H, NH); Mass (m/z) 438 (M^{+}). The authentic sample also obtained from the reaction of 5',6-anhydro-2',3'-isopropylidene-6-hydroxyluridine[7] with phenylselenenyl chloride (PhSeCl) and silver trifluoroacetate ($AgOCOCF_3$) in acetonitrile in quantitative yield.
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