

EFFICIENT PHENYLSULFENYLATION AND PHENYLSELENENYLATION AT THE 5-POSITION OF URACIL NUCLEOSIDES WITH DISULFIDE AND DISELENIDE MEDIATED BY [BIS(TRIFLUOROACETOXY)IODO]BENZENE

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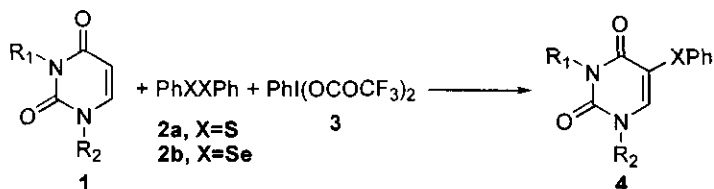
Abstract - A series of uracil nucleosides reacted with diphenyl disulfide or diphenyl diselenide in the presence of hypervalent iodine reagent, [bis(trifluoroacetoxy)iodo]benzene, in acetonitrile to give the corresponding C-5 phenylsulfenylated or phenylselenenylated products respectively in excellent yields.

5-Substituted uridines constitute a class of biologically important molecules both in terms of their chemotherapeutic activities¹ and synthetic oligonucleoside probes.² A variety of synthetic methods for the introduction of sulfide and selenide functional groups in nucleoside have been developed due to their significant importance in bioscience and organic synthesis. The organosulfide and selenide functional groups at the C-5 position of pyrimidine nucleosides have been known as useful tools for various functional group transformation reactions due to their unique properties.³ Pyrimidine nucleosides substituted at C-5 by thioether groups have been investigated as a chemotherapeutic drug candidate for antiviral agent⁴ and useful intermediate for various functional group transformations.⁵ Several efforts for introducing sulfenyl or selenenyl group to pyrimidine nucleosides have been reported by 5-lithiation method,⁶ 5-chloromercuration followed by palladium catalyzed coupling reaction⁷ and silver agent with sulfenyl chloride or selenenyl chloride.^{8a}

Although a number of synthetic routes to pyrimidine bases or nucleosides substituted at C-5 by phenylsulfide and phenylselenide groups have appeared in the literature⁶⁻⁹ concerning phenylsulfenylation an improved method has been required because of the relatively low yield in C-5 sulfenylation. Recently, Ochiai *et al.*,¹⁰ Stang *et al.*,^{11a,b} and Chen *et al.*^{11c} have developed the new hypervalent iodonium salts which are available for the nucleophilic substitution of alkenyl or alkynyl or phosphorodithionates substrates. Direct nucleophilic sulfenylation with thiophenol at the *ortho* position of electron-rich

phenol ethers using the hypervalent iodine reagent, [bis(trifluoroacetoxy)iodo]benzene (BTIB) has been reported.^{12a} Also, electrophilic reaction of bis(phenylthio)iodobenzene with 1-alkyne has been developed to give 1,2-bis(arylthio)alkenes.^{12b} In the course of our study on the functionalization of pyrimidine nucleoside, we have found that various uracil nucleosides reacted with diphenyl disulfide or diphenyl diselenide in the presence of BTIB ($\text{PhI}(\text{OCOCF}_3)_2$) in MeCN to afford the C-5 phenylsulfenylated or C-5 phenylselenenylated products respectively in excellent yield. This work has an advantage over our previous work⁸ in which phenylsulfenyl chloride and silver acetate are used.

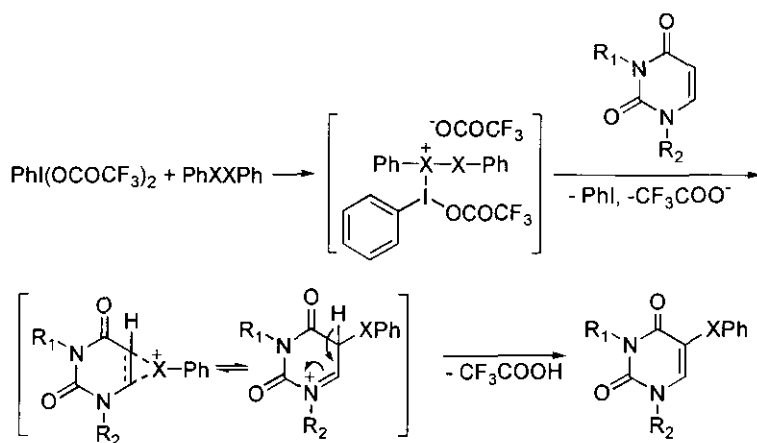
Table 1. Phenylsulfenylation and phenylselenenylation at the C-5 position of uracil nucleosides.



Run	R ₁	R ₂	Solvent	X	Temp	Time(h)	Yield(%) ^{a)}	Ref
1	H	H	MeCN	Se	rt	0.2	81	17
2				S	refl	3	87	17
3	Me	Me	MeCN	Se	rt	0.2	99	16
4				S	refl	2	81	17
5	H	Rib(OAc) ₃	MeCN	Se	rt	0.2	97	17
6			MeOH	S	refl	3	trace	
7			THF	S	refl	3	trace	
8			Cl-CH ₂ -CH ₂ -Cl	S	refl	2	48	17
9			MeCN	S	refl	2	82	17
10	H	Rib(OBz) ₃	MeCN	Se	rt	0.2	95	17
11				S	refl	2	95	17
12				Se	rt	0.2	94	16
13	H		MeCN	S	refl	2	80	17
14	H		MeCN	Se	rt	0.2	92	17
15	H		MeCN	S	refl	2	93	17
16	H		MeCN	Se	rt	0.2	97	17
17	H		MeCN	Se	rt	0.2	99	8a

^{a)} Isolated yields; molar ratio X=Se, **1** / **2** / **3** = 1 / 0.7 / 0.7; X=S, **1** / **2** / **3** = 1 / 1 / 2

Phenylsulfenyl chloride is unstable and difficult to be purified. When thiol was used instead of disulfide, the reaction did not proceed under same reaction conditions. As a model reaction, phenylsulfenylations of 2',3',5'-triacetyluridine was performed with **2a** and **3** under reflux in various solvents. The sulfenylation strongly depends on solvents used. Treatment of 2',3',5'-triacetyluridine with 1.0 eq. of **2a** and 2.0 eq. of **3** in acetonitrile afforded the corresponding 5-sulfenylated product (**4a**) in good yield (Run 9, 82 %). While the same reaction with **2b** resulted in rapid formation of **4b** quantitatively (Run 5, 97 %) within 10 min. However, the use of 1,2-dichloroethane as a solvent suppressed the reaction (Run 8, 48 %). Both tetrahydrofuran and methanol gave a traceable amount of the sulfenylated product. The results obtained are summarized in Table 1. The generality of this procedure was indicated by the reaction with three types of uracil nucleosides of uracils, protected uridines and protected acyclic uracil nucleosides. As shown in Table 1, the reaction rate of phenylselenenylation was much faster than phenylsulfenylation. It was postulated that formation of selenium cation intermediate was much easier than sulfonium cation intermediate¹³. These direct arylsulfenylations and arylselenenylations are regioselective at the C-5 position of uracil nucleosides. The 6-substituted products were not detected in all the cases. Phenylselenenylation was accomplished within 10 minutes by the reaction with 0.7 equivalent of diphenyl diselenide and 0.7 equivalent of BTIB at room temperature. In the case of phenylsulfenylation, the use of 1.0 equivalent of diphenyl disulfide and 2.0 equivalent of BTIB afforded higher yields. Though the reaction mechanism is not yet clear, a possible mechanism is postulated in Scheme 1. It is considered that diphenyl disulfide or diphenyl diselenide is activated by the actions of PIFA to afford the highly electrophilic sulfonium or selenium cation intermediate and subsequent formation of episulfonium³ or selenium salt^{8, 14, 15} followed by generation of double bond between C-5 and C-6.



Scheme 1. Possible mechanism for phenylsulfenylation and phenylselenenylation at C-5 position of uracil nucleosides.

The characteristic points of the present reactions are (i) diphenyl disulfide (diphenyl diselenide), which is easily available can be used as electrophile, (ii) the reaction can be performed under mild conditions, (iii) the hypervalent iodine reagent is simpler and safer than general metallic reagents (iv) the reaction shows high regioselectivity.

In summary, regioselective phenylsulfenylation or phenylselenenylation of uracil nucleosides at C-5 has been successfully achieved by the reaction with diphenyl disulfide or diphenyl diselenide in the presence of **3** in acetonitrile in excellent yields.

A typical experimental procedure is as follows : A mixture of 2',3',5'-triacetyluridine (111 mg, 0.30 mmol), diphenyl diselenide (65 mg, 0.21 mmol) and [bis(trifluoroacetoxy)iodo]benzene (90 mg, 0.21 mmol) was stirred at 25 °C in acetonitrile under nitrogen atmosphere. After being stirred for several min, the reaction mixture was poured into 10 mL of water and partitioned with 20 mL of dichloromethane. The organic layer was washed with 5 % sodium bicarbonate solution (10 mL x 2), brine (10 mL), then dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure to afford a yellow solid. The crude product was purified by flash column chromatograph (silica gel, 230-400 mesh, EtOAc : Hexane = 2 : 1) to give 2',3',5'-triacetyl (5-phenylseleno)uridine (153 mg, 97 %); ¹H NMR (200 MHz, CDCl₃) δ 9.25 (s, 1H, N3), 7.72 (s, 1H, C6), 7.23-7.47 (m, 5H, Ph), 6.06 (d, *J* = 4.9 Hz, 1H, C1'), 5.26 (m, 2H, C2',C3'), 4.24 (m, 3H, C4',C5'), 2.08 (m, 9H, 3Ac), ¹³C NMR (75 MHz, CDCl₃) δ 170.1, 169.9, 161.1, 150.1, 142.9, 132.2, 129.5, 129.1, 127.8, 105.5, 87.2, 80.1, 77.4, 77.0, 76.6, 72.9, 70.4, 63.1, 20.7, 20.6, 20.3, MS (relative intensity) 526 (M⁺, 23.4), 466 (32.9), 259 (97.8), 187 (48.6), 157 (54.3), 139 (100), 117 (80.4), 97 (91.2); 2',3',5'-triacetyl (5-phenylthio)uridine (118 mg, 82 %); ¹H NMR (200 MHz, CDCl₃) δ 8.37 (s, 1H, N3), 7.90 (s, 1H, C6), 7.27 (m, 5H, Ph), 6.08 (d, *J* = 4.8 Hz, 1H, C1'), 5.32 (m, 2H, C2',C3'), 4.31 (m, 3H, C4',C5'), 2.09 (m, 9H, 3Ac), ¹³C NMR (75 MHz, CDCl₃) δ 169.8, 169.3, 160.6, 149.7, 143.4, 134.1, 131.1, 128.9, 128.3, 126.6, 108.4, 87.2, 80.0, 72.9, 70.1, 62.9, 20.6, 20.4, 20.3; MS (relative intensity) 478 (M⁺, 12.9), 418 (7.2), 259 (100), 220 (11.9), 157 (15.9), 149 (13.4), 139 (97.8), 97 (49.1).

All the products were identified by comparison with their MS, ¹H or ¹³C NMR spectra with those from the literature data.^{8a, 16, 17}

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