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Synthesis of selenium- and tellurium-containing nucleosides derived from uridine

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ABSTRACT

The synthesis of selenium- and tellurium-containing nucleosides, derived from uridine is described herein. These compounds were prepared in a concise and short synthetic route in good yields, by nucleophilic substitution of a tosylate group by organoselenium nucleophiles.

The synthesis of selenium derivatives of biologically important molecules has gained increasing attention over the past years, since the discovery that selenium is a nutritionally essential trace element for humans.[1] It is found in a number of selenoproteins and selenopeptides, particularly in the form of the amino acid selenocysteine.[2] It is also known that the selenium atom plays a key role in the mode of action of such proteins, which cannot be played by its closest relative, sulfur.[3] Moreover, organoselenium compounds have been found to function as antioxidants, chemoprotectors, apoptosis inducers, and chemopreventors in several organs such as brain, liver, skin, colon, lung, and prostate.[4] In this context, the synthesis of selenium-modified nucleosides has attracted attention[5] and selenoanhydronucleosides,[6] deoxynucleosides selenocyanates,[7] phosporoselenoate nucleosides,[8] and 4'-selenonucleosides[9] have been described. Moreover, selenium-containing nucleosides with interesting biological activities were also reported. For example, 6-(phenylselenenyl)pyrimidine nucleosides display in vitro activity against HIV-1 (human immunodeficiency virus type-1) and HIV-2 (human immunodeficiency virus type-1) in primary human lymphocytes,[10] while oxaselenolane nucleosides were also described to have potent HIV-1 and HBV (hepatitis B virus) activities.[11] In addition, selenium-containing nucleosides have been used as a synthetic handle for the synthesis of deoxynucleosides[12] and the replacement of an oxygen atom in nucleotides by selenium is largely used in the determination of 3-D structures of DNA and RNA, by X-ray crystallography using MAD (multiwavelength anomalous dispersion).[13] In MAD experiments, selenium serves as an effective anomalous scattering center and greatly facilitates phase determination of crystals, thus allowing a high-resolution determination of the structure of the nucleic acids.[14]

On the other hand, the tellurium derivatives of nucleosides have been largely overlooked and only scarce reports have appeared in the literature,[6] despite the fact that, in many cases they were shown to be more effective antioxidants and chemoprotectors than their corresponding selenium and sulfur analogs.[15]

Stimulated by our recent work on the synthesis of chiral selenium-containing non-natural amino acids and peptides,[16] including selenocysteine[17] and more recently, on chiral telluroamino acids that possess strong glutathione peroxidase-like (GPx-like) activity,[18] we decided to expand our interest to the introduction of an organochalcogen moiety in the nucleoside framework. To accomplish this task, we sought to functionalize the 5′-position of uridine with an organochalcogen group. This would be

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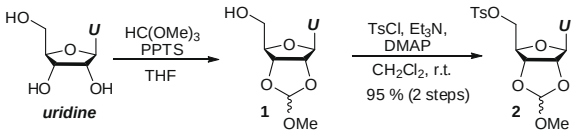


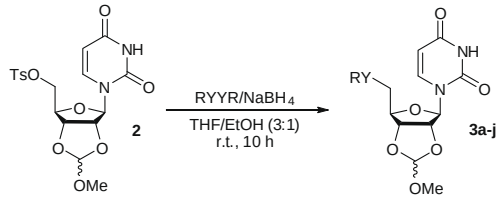
Scheme 1. Synthesis of tosylate **2** (*U* = uracil).

accomplished by nucleophilic substitution of an appropriate leaving group, obtained by activation of the 5′-hydroxyl at a protected uridine derivative.

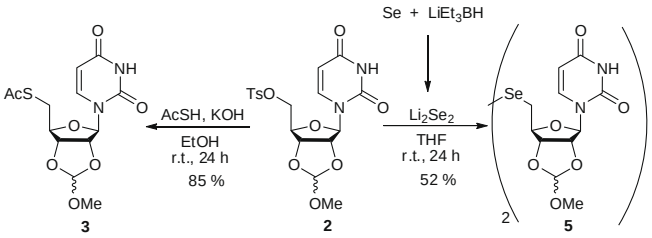
As delineated in our synthesis plan, the success of our strategy was closely linked to an efficient activation of the 5′-hydroxyl group in uridine. Thus, based on our previous experience on the nucleophilic substitution of a tosylate group by chalcogen nucleophiles,[19] we decided to transform the 5′-hydroxyl group in their corresponding *p*-toluenesulfonate ester, as already described by Poulter et al.[20] First, appropriate protection of the secondary hydroxyl groups of uridine was needed and this was accomplished by reaction with trimethylorthoformate, in the presence of PPTS, to afford the corresponding 2',3'-methoxymethylidene derivative **1**. The protected uridine **1** was treated, without purification, with *p*-toluenesulfonyl chloride, in the presence of DMAP and Et_3N, to smoothly provide the required 5'-OTs uridine in an excellent 95 % yield, for the two steps (Scheme 1).[20]

With the required tosylate **2** in hand, we turned our attention to the introduction of the organochalcogen moiety by nucleophilic displacement. Pleasingly, we found that treatment of **2** with phenylselenide anion, generated by reduction of diphenyl diselenide with sodium borohydride, afforded the desired 5'-phenylseleno nucleoside **3a** in good yield, using a mixture of THF and ethanol as solvent (Table 1, entry 1). Extension of these conditions to a broader range of selenium nucleophiles proved to be viable, and the reaction with the nucleophile derived from $(4\text{-ClPhSe})_2$ afforded the corresponding selenium-containing uridine derivative **3b** in 72% yield (entry 2). Aliphatic diselenides, where R groups were Bn, *n*-Bu, and Et, were also evaluated as the nucleophilic source and products **3c–e** were obtained in good yields (entries 3–5). In order to expand the scope of the methodology to other chalcogens, we decided to prepare tellurium derivatives of uridine. This was accomplished in the same way as for the selenium derivatives, and cleavage of diorganoditellurides with $NaBH_4$, followed by reaction with tosylate **2** smoothly provides the corresponding telluronucleosides **3f–i** in good yields (entries 6–9). Again, the reaction

Table 1
Synthesis of selenium- and tellurium-containing nucleosides



Entry	RYYR	RY	Yield (%)
1	$(PhSe)_2$	PhSe	75
2	$(4\text{-ClPhSe})_2$	4-ClPhSe	72
3	$(PhCH_2Se)_2$	$PhCH_2Se$	70
4	$(n\text{-BuSe})_2$	*n*-BuSe	70
5	$(EtSe)_2$	EtSe	67
6	$(PhTe)_2$	PhTe	78
7	$(4\text{-ClPhTe})_2$	4-ClPhTe	65
8	$(4\text{-MeOPhTe})_2$	4-MeOPhTe	60
9	$(n\text{-BuTe})_2$	*n*-BuTe	76
10	$(PhS)_2$	PhS	77



Scheme 2. Syntheses of **3** and **5**.

is applicable to both aromatic and aliphatic tellurium nucleophiles. Also, the reduction of $(PhS)_2$ with $NaBH_4$, followed by reaction with **2**, under our standard conditions, furnished the sulfur derivative in 77 % yield (entry 10).[21]

Finally, treatment of tosylate **2** with thioacetic acid, under basic conditions, afforded the corresponding thioacetate in 85 % yield (Scheme 2). In addition, reaction of **2** with lithium diselenide, generated in situ by the reaction of elemental selenium with super-hydride,[22,23] smoothly afforded the desired diselenide in a moderate 52 % yield (Scheme 2).[24]

In summary, we have described herein the synthesis of selenium- and tellurium-containing nucleosides, derived from uridine in a concise and short synthetic route in good yields. Additionally, the organochalcogen moiety might serve as a synthetic handle for the synthesis of deoxynucleosides and, more importantly, we believe that it might display GPx-like activity.

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Supplementary data

Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.164.

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21. *General procedure for the preparation of* **3a–j**: Under an argon atmosphere, sodium borohydride was added to a solution of the dichalcogenide (0.55 mmol) in THF (4 mL). Ethanol (2 mL) was then added dropwise and the clear solution formed was stirred at room temperature for 10 min. After this time a solution of tosylate (0.440 g, 1 mmol) in THF (1 mL) was added dropwise. The resulting solution was stirred for 24 h at room temperature. The mixture was quenched with a saturated NH_4Cl solution (10 mL), extracted with CH_2Cl_2, and the combined organic fractions were collected, dried over $MgSO_4$, and filtered, the solvent was removed in vacuo. The crude product was purified by flash chromatography first eluting with hexanes and then with a mixture of hexanes/ethyl acetate (80:20). *Representative analytical data for* **3a:** Yield: 75%; RMN ^1H ($CDCl_3$, 200 MHz, ppm) for diastereomers A and B (ratio **91:9**) δ 10.42 (s, 1H), 7.55–7.19 (m, 6H), 6.00 and 5.95 (s, 1H), 5.70 (d, J = 7.9 Hz 1H), 5.56 (d, J = 2.5 Hz 1H), 5.12–4.96 (m, 2H), 4.32–4.24 (m, 1H), 3.29–3.22 (m, 5H); RMN ^{13}C ($CDCl_3$, 50 MHz, ppm) δ 163.9; 149.9; 142.8; 132.8; 128.9; 127.1; 119,0; 118.0; 102.3; 95.8; 94.1; 86.6; 84.3; 83.4; 52.3; 51,2; 29,6; IV (cm^{-1}) 3170, 3057, 2939, 2832, 1685, 1577, 1454, 1378, 1270, 1121, 1075. HRMS-ESI: *m/z* calcd for $C_{17}H_{18}N_2O_6Se + Na^+$: 449.0227; found: 449.0222.
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23. Under an argon atmosphere, lithium diselenide was generated by reaction of gray elemental selenium (0.0948 g, 1.2 mmol) with lithium triethylborohydride (1.2 mL, 1.2 mmol) in dry THF (5 mL). The suspension was allowed to stir for at least 20 min, and a THF (10 mL) solution of tosylate **2** (0.440 g, 1.0 mmol) was added dropwise within 20 min. The resulting solution was stirred for 24 h at room temperature. The mixture was quenched with a saturated NH_4Cl solution (20 mL), extracted with CH_2Cl_2, and the combined organic fractions were collected, dried over $MgSO_4$, and filtered, the solvent was removed in vacuo. The crude product was purified by flash chromatography (hexane:ethyl acetate 80:20). Drying in vacuo afforded the diselenide **5.** Analytical data for **5**: Yield: 52%; RMN ^1H ($CDCl_3$, 200 MHz, ppm) for diastereomers A and B (ratio **91:9**) δ 10.29 (s, 1H), 7.35 (d, J = 8.0 Hz, 1H), 5.99 and 5.91 (s, 1H), 5.76 (d, J = 7.6 Hz, 1H), 5.68 (s, 1H), 5.16 (d, J = 7.0 Hz, 1H), 4.93–4.88 (m, 1H), 4.54 (d, J = 3.6 Hz, 1H), 3.39–3.30 (m, 5H); ^{13}C ($CDCl_3$, 50 MHz, ppm) 163.8; 150.1; 143.4; 119.0; 102.6; 96.8; 87.9; 84.4; 83.6; 52.7; 51.2; 32.1; IV (cm^{-1}) 3175, 3057, 2939, 2832, 1695, 1459, 1372, 1270, 1127, 1081, 983, 819. HRMS-ESI: *m/z* calcd for $C_{22}H_{26}N_4O_{12}Se_2 + Na^+$: 720.9775; found: 720.9769.
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