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New Nucleoside Heteroanalogues: Desoxynucleoside Selenocyanates[1]

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Abstract: *New nucleoside heteroanalogues, 5'- and 3'-desoxynucleoside selenocyanates and primary desoxysugar selenocyanates, were synthesized from activated nucleoside and sugar derivatives and a new convenient seleno nucleophile, tetrabutylammonium selenocyanate. Tresylate-based activation of hydroxy functions turned out to be most successful for formation of these selenocyanates compared with mesylate- or triflate-based activation.*

Seleno derivatives of saccharides and nucleosides are often used as synthetic precursors for further modification of these biologically significant compounds.[2a-e] However, biologically active species based on the formal displacement of a hydroxy group by a seleno function have still not been developed, partly due to difficulties in the preparation of non-trivial seleno derivatives. Indeed, the closest seleno analogue of a hydroxy group is a selenol function. However, selenols are extremely unstable toward oxidation and therefore not useable. In general, PhSe or, more rarely, AlkSe derivatives are the simplest most often used seleno desoxysaccharides and desoxynucleosides.[2a-e] Yet it is difficult to consider these compounds as potential substrate analogues of enzymes involved in sugar and nucleoside biotransformations, due to strength of the Ph–Se bond and the bulk of the phenyl group.

Simple alkyl selenocyanates were shown to possess powerful anticancer activity[3-5] being involved in DNA and RNA biosynthesis.[5] Therefore nucleoside selenocyanates are of interest in anticancer drug design. Though the biochemical mechanism of selenocyanate action remains unknown, it was proposed that selenocyanate biotransformation products are important.[3] Since selenocyanates are reduced *in vivo* to selenols,[3] such desoxyhexose and desoxypentose derivatives could be considered as a masked form of sugar and nucleoside selenols.

No general synthetic route to desoxysugar selenocyanates is known. A primary selenocyanate has been obtained recently *via* ring-opening of the β-D-altrofuranose 5'-*O*-6'-*O*-sulphoester by potassium selenocyanate.[6]

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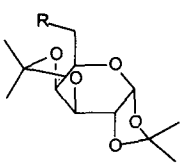
Another example is the preparation of two secondary selenocyanates from the corresponding desoxyhalosugars using still exotic Mo-complexes.[7] We describe herein a simple and mild method for preparation of sugar/nucleoside selenocyanates starting from trivially protected saccharides and nucleosides.

We found that interaction of activated derivatives of a primary saccharide hydroxy group as well as of the secondary 3'-OH group of 2'-desoxynucleosides with selenocyanate nucleophiles (see below) at low or ambient temperatures leads to formation of corresponding selenocyanates in moderate or high yields.

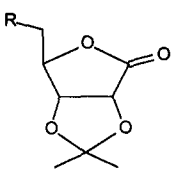
Activated hydroxy derivatives [triflates, tresylates (trifluoroethyl sulphonates) and mesylates; see Schemes below] were obtained in near quantitative yields from the corresponding hydroxy compounds and triflic anhydride, tresyl or mesyl chlorides respectively, in $CHCl_3$ or CH_2Cl_2 in the presence of Py at -30^0 for triflates and at -10^0 for tresylates and mesylates.

The organosoluble NBu_4SeCN[8] (**1**) was used as the nucleophile and all reactions were performed under an argon atmosphere using a 2-4-fold excess of **1**. This new reagent proved to be more successful than potassium selenocyanate providing better yields and lower side-product formation in the reaction of nucleoside tresylates in DMF (see below). Moreover, this salt is quite soluble in slightly polar solvents (*e.g.*, $CHCl_3$) in which it leads to higher yields compared with reactions in DMF.

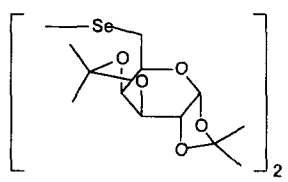
Primary selenocyanates. Mesylate **2d** turned out to be unreactive when heated with **1** in $CHCl_3$ under reflux or in DMF at 70^0. Also galactose **2e** was inert in the Mitsunobu reaction with diethyl azodicarboxylate – triphenylphosphine (THF, 0^0). In contrast, selenocyanates **2c** and **3c** were formed from triflates **2b** and **3b** (CH_2Cl_2, 25^0) in 70% and 87% yields, respectively. Tresylate **3a** was converted quantitatively with **1** ($CHCl_3$, reflux, 24 h) into seleno compound **3c**. Disappearance of tresylate **2a** under the same conditions occurred within 12 days and resulted in formation of selenocyanate **2c** and diselenide **4** in 50% and 46% yields, respectively. We conclude that the reaction of the bulky nucleophile **1** is quite susceptible to steric hindrance in the substrate (see also results for secondary selenocyanates below).



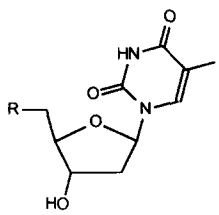
2a-e
a: R = TresO
b: R = TfO
c: R = SeCN
d: R = MsO
e: R = OH



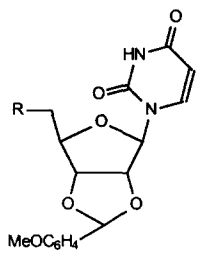
3a-c
a: R = TresO
b: R = TfO
c: R = SeCN



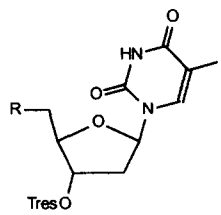
In the case of nucleosides only tresylates are convenient selenocyanate precursors. For instance, interaction of triflate **5c** with **1** ($CHCl_3$, -40^0) leads to formation of a multicomponent mixture and no corresponding selenocyanate product was detected. When tresylates **5a, 6a, 7a** and **8a** were treated with **1** ($CHCl_3$, 25^0, 24 h), the corresponding selenocyanates **5b, 6b, 7b** and **8b** were isolated (for yields see Scheme below). The yields were 15-20% lower when the reaction was carried out in DMF and formation of selenocyanate **5b** occurred only in 25% yield if potassium selenocyanate was used (DMF, 25^0, 45 h).



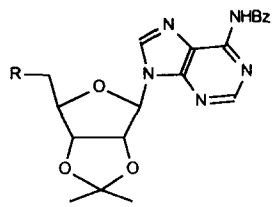
5a: R = TresO
5b: R = SeCN (77%)
5c: R = TfO



6a: R = TresO
6b: R = SeCN (40%)

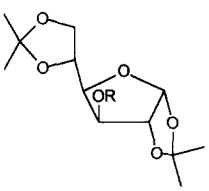


7a: R = TresO
7b: R = SeCN (21%)

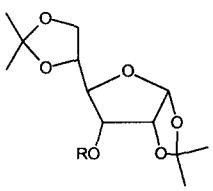


8a: R = TresO
8b: R = SeCN (45%)

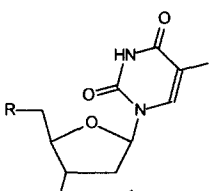
Secondary selenocyanates. Steric crowding at the electrophilic center blocks reaction of the nucleophile **1** with secondary sulphonates. Triflates **9a** and **10a** ($CHCl_3$, 25°, 24 h) as well as tresylate **9b** (DMF, 70°, 5 h) and mesylate **9c** (DMF, 70°, 24 h) remained unchanged when treated with **1**. Likewise, no reaction with **1** was observed using PPh_3 – CCl_4 based activation[9] of hydroxy compound **10b** (THF, reflux). However, interaction of the less hindered nucleoside tresylates **11a** and **12a** with nucleophile **1** ($CHCl_3$, reflux, 24 h) led to the desired selenocyanates **12b** and **11b** in 55% and 20%, respectively (the relative configuration of substituents has been established *via* NOESY experiments in CD_3COCD_3). In contrast, mesylate **11d** did not interact with **1** (DMF, 60°. 24 h), while triflate **11c** was transformed in the presence of **1** (CH_2Cl_2; –30°) into a complex mixture. Thus, for preparation of nucleoside selenocyanates *tresylate-based activation is a successful compromise between the highly reactive triflates and the unreactive mesylates.*



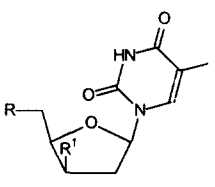
9a: R = Tf
9b: R = Tres
9c: R = Ms



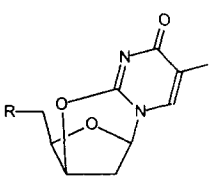
10a: R = Tf
10b: R = H



12a: R^1 = TresO, R = TBSO
12b: R^1 = SeCN, R = TrO



11a: R^1 = TresO, R = TrO
11b: R^1 = SeCN, R = TBSO
11c: R^1 = TfO, R = TrO
11d: R^1 = MsO, R = TrO

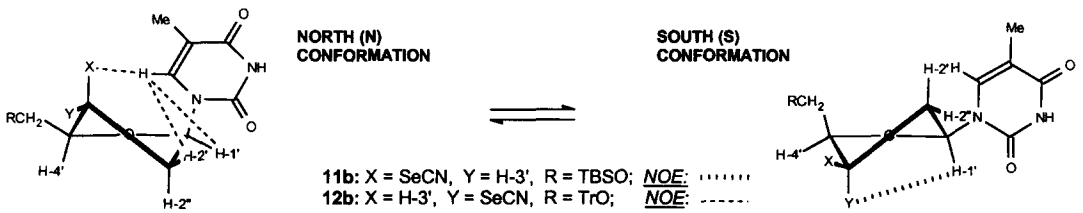


13: R = TBSO

In the case of transformation of **12a** the side product **13** was also isolated in 68% yield. Since the weak electrophile **13** did not interact with **1** under reaction conditions and no transformation to **13** occurred under these conditions for a mixture of **11b** and **1**, it is obvious that compound **13** is formed from **12a** in parallel with selenocyanate **11b**. We conclude therefore that the higher yield of selenocyanate formed from the 3'-β-substituted substrate **11a** is due to unfavorable intramolecular cyclization of the latter. In addition, the 1',3',4'-tri-β-substituted **11a** is less hindered for the α-attack of selenocyanate anion than the 3'-α-1'-β-4'-β-trisubstituted **12a** for β-attack.

NOESY spectra of desoxynucleoside selenocyanates **11b** and **12b** permit one to estimate qualitatively a S↔N conformational equilibrium[10,11] for these compounds (see the Scheme below for selected NOE interactions). The N-conformation of the desoxyribose ring and the *anti*-conformation of the nucleobase are

significantly populated for **12b** as deduced from the observed NOE interaction between the olefinic proton of the pyrimidine ring and the H-3'-furanose proton. We conclude also that the amount of the S-form for **11b** is not low since a NOE interaction between the H-1' and H-3' protons is detected. These conclusions for **12b** and **11b** are in agreement with the concept of "the 3'-substituent electronegativity dictate"[10] and with the analysis of the steric effect role for the S↔N equilibrium in 3'-β-substituted 3'-desoxynucleosides,[11] respectively.



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