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Isothiocyanatoulosonates, a new type of glycosyl isothiocyanate useful for the stereocontrolled synthesis of thiohydantoin spironucleosides

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Abstract—Thiohydantoin spironucleosides and *N*-alkyl, aryl and glycosyl derivatives are prepared in a stereocontrolled manner, by reaction of ammonia, and of alkyl-, aryl- and glycosyl-amines with a new class of isothiocyanato sugar: the methyl 2-deoxy-2-isothiocyanatohex-2-ulofura(pyra)nosonates. The reaction produces an intermediate thioureido derivative, which spontaneously cyclates to give the spironucleoside in high yield. Alternatively, the same spironucleosides are prepared from methyl 2-amino-2-deoxy-hex-2-ulofura(pyra)nosonates and alkyl-, aryl- and glycosyl isothiocyanates. Some of the prepared compounds have the structure of *N*-nucleoside of spirothiohydantoins.

The isothiocyanates are synthetic intermediates with wide versatility. The strong electrophilicity of the NCS group enables the isothiocyanates to participate in addition and cycloaddition reactions, and these heterocumulenes are especially useful in heterocyclic syntheses.[1] In the last two decades, isothiocyanato derivatives of sugars, mainly aldopyranosyl isothiocyanates, have been widely used in the synthesis of different glycoconjugates of biological importance,[2] such as thioureidosugars,[3] *N*-glycopeptides,[4] *N*-nucleosides,[5] spiro-*C*-glycosides and spironucleosides of 1,3-*O*,*N*-heterocycles.[6] Aldopyranosyl isothiocyanates have also been used to prepare glycodendrimers and glycoclusters of interest in supramolecular chemistry.[7]

At the same time, in the last few years the chemistry of spironucleosides has been strongly developed,[8] due to the isolation, from *Streptomyces hygroscopicus*, in 1991 of the first natural spironucleoside, the (+)-hydantocidin, a furanoid spirohydantoin[9] with potent herbicidal and regulatory plant growth activities and low toxicity for mammals.[10]

In this communication, we describe the preparation of a new class of glycosyl isothiocyanates, the methyl 2-deoxy-2-isothiocyanatohex-2-ulofura(pyra)nosonates, which are used in the syntheses of 7-thio analogues of hydantocidin. We have previously shown[6] that ketofuranosyl isothiocyanates are transient intermediates in the preparation of furanoid and pyranoid spirooxazolidines. Data on 2-deoxy-2-thiocyanatoulosononitriles have been recently reported.[11]

The starting materials to prepare the ketose glycosyl isothiocyanate derivatives **6**, **7** and **10** are the β-D-psicofuranosyl (**1**) and β-D-fructopyranosyl (**2**) azides, which are easily available from the corresponding sugar spiroketals.[6,12] Simultaneous oxidations of the hydroxymethyl and benzyl groups of **1** with ruthenium chloride–sodium metaperiodate[13] (→**3**) followed by esterification with diazomethane gave the methyl 5-*O*-benzoyl-β-azido ulosonate **4** (Scheme 1), which by catalytic hydrogenation produced the D-psicofuranosylamine derivative **5**, as a pair of anomers, in a virtually quantitative yield. The formation of **5** was monitored by chromatography, and initially the major compound was the β-anomer, but anomerization took place and after 20 min the α-anomer became the major compound. For evidence of the anomeric configuration, see below. Anomerization of related glycosylamines has been reported.[14] Reaction of the mixture of anomers **5** with thiophosgene in basic medium gave the methyl 2-deoxy-2-isothiocyanato-α (**6**) and -β (**7**) D-*ribo*hexulofuranosonates as major (65% from **5**) and minor (20% from **5**) compounds, respectively.[15] The NCS groups of **6** and **7** were evident from their IR absorptions at 2018 and 2016 cm^{-1} and from the ^{13}C resonances at $\cong$145 ppm.[16]

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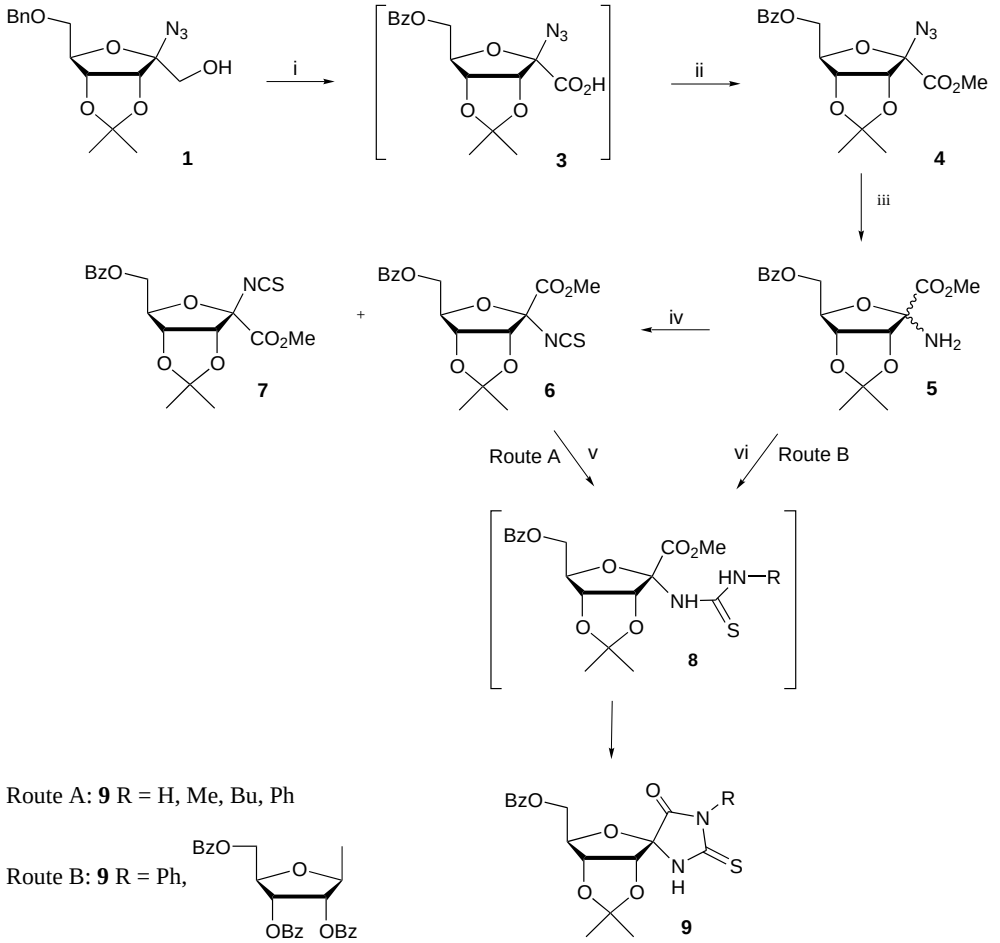
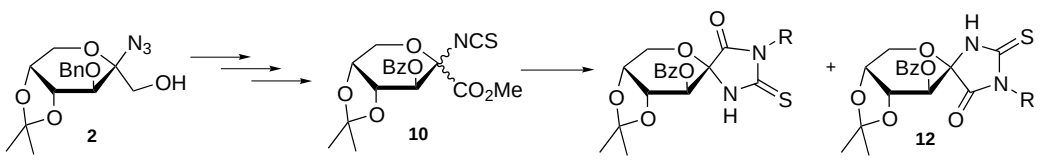


Scheme 1. *Reagents and conditions*: (i) $RuCl_3 \cdot H_2O$, $NaIO_4$, rt, 15 min; (ii) CH_2N_2, MeOH:Et_2O, 0°C, 20 min. Yield 45% from **1**; (iii) H_2/Pd–C, rt, 30 min. Yield 95%; (iv) Cl_2CS, $CaCO_3$, $CHCl_3$:H_2O, rt, 3 days. Yield 65% for **6** and 20% for **7**; (v) RNH_2, THF (or THF:H_2O), rt, 10 min. Yield 90–95%; (vi) RNCS, THF, 40°C, 1–3 days, 83–90%.



Scheme 2. *Reagents and conditions*: as in Scheme 1.

The anomeric configuration was supported on the value of $^3J_{CH}$ between C-1 and H-3; this value (1.6 Hz) in compound **6** was in the range for *syn*periplanar nuclei, whereas in **7** (7.9 Hz) it was close to the value for nuclei in *trans*-relationship.[17,18] The $^3J_{HH}$ values for the sugar moieties of **5β** and **7** were similar to the corresponding values for the β-psicofuranosyl azide **1**.[12] The anomeric carbon C-2 of **5α** and **7** resonated at lower field than that for **5β** and **6**, as in related pairs of anomers.[14a,b]

Reactions of **6** with ammonia, alkyl and aryl amines (Scheme 1, Route A) gave the corresponding thioureido derivatives **8**, which spontaneously cyclates in the reaction medium, and under mild conditions, to afford the corresponding spironucleoside of thiohydantoin **9** in quantitative yield (from **6**). Alternatively, compounds **9** were obtained by reaction of **5** with isothiocyanates (Scheme 1, Route B); when a D-ribofuranosyl isothiocyanate was used, the spirohydantoin **9** has a glycosyl radical on N-8, consequently its structure is simultaneously that of *N*- and spironucleoside.[19] In Route B, due to the anomeric equilibrium of the glycosylamine **5**, resoluble mixtures of C-5 epimers of **9** were obtained.

In a similar way starting from the 3-*O*-benzyl-β-D-fructopyranosylazide **2**, the pyranoid 5-*O*-benzoyl-spirothiohydantoins **11** and **12** were obtained (Scheme 2).

In conclusion, a short, versatile, and efficient procedure to prepare methyl 2-deoxy-2-isothiocyanato-hex-2-ulofura(pyra)nosonates, a new class of glycosyl isothiocyanate, is reported. These compounds are easily transformed, under mild conditions into spirothiohydantoins. The scope and limitations of the method are currently under study in our laboratory.

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15. Selected data for **6**: $[\alpha]_D^{28}$ −62 (*c* 0.9, CH_2Cl_2); IR λ_{max} 2986, 2018, 1757, 1724, 1601, 1271 and 1099 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04–7.45 (m, 5H, Ph), 5.07 (d, 1H, $J_{3,4}=6.8$, H-3), 4.84 (dd, 1H, $J_{4,5}=3.1$, H-4), 4.68 (m, 1H, H-5), 4.58 (dd, 1H, $J_{5,6a}=3.8$, $J_{6a,6b}=12.2$, H-6a), 4.49 (dd, 1H, $J_{5,6b}=4.2$, H-6b), 3.80 (s, 3H, OCH_3), 1.71 and 1.40 ppm (each s, each 3H, $2CH_3$; ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 166.0 (CO_2Me), 165.9 (OBz), 144.9 (NCS), 133.5–128.2 (6C, Ph), 117.4 [$C(CH_3)_2$], 95.1 (C-2), 84.4 (C-3), 82.6 (C-5), 80.9 (C-4), 63.5 (C-6), 53.8 (OCH_3), 26.1 and 25.3 (2 CH_3) ppm; HRCIMS *m*/*z* obsd 394.0959 calcd for $C_{18}H_{20}NO_7S$ 394.0960.
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18. For similar configurational assignments on related pyranoid spirohydantoins see Refs. 8c and 8d.
19. Selected data for **9**, R = 2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl. $[\alpha]_D^{27}$ −47 (*c* 1.0 CH_2Cl_2); IR λ_{max} 3030, 2996, 2948, 1773, 1724, 1601, 1269 and 1099 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13–7.34 (m, 21H, 5 Ph, NH), 6.48 (d, 1H, $J_{1',2'}=3.0$, H-1′), 6.28 (dd, 1H, $J_{2',3'}=6.5$, H-2′), 6.20 (t, 1H, $J_{3',4'}=6.5$, H-3′), 4.89 (dd, 1H, $J_{4',5'a'}=3.6$, $J_{5'a',5'b'}=12.2$, H-5′a), 4.75 (dd, 1H, $J_{2,3}=2.4$, $J_{3,4}=6.0$, H-3), 4.65 (ddd, 1H, $J_{4',5'b}=4.8$, H-4′), 4.63 (d, 1H, H-4), 4.57 (td, 1H, $J_{2,CH_2}=6.0$, H-2), 4.53 (dd, 1H, H-5′b), 4.53 (m, 2H, CH_2OBz), 1.58, 1.33 ppm (each s, each 3H, $2CH_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 181.2 (C-6), 169.9 (C-9), 166.1, 166.0, 165.0 (2C) (4OBz), 133.5–128.2 (24 C, Ph), 114.6 [$C(CH_3)_2$], 92.1 (C-5), 86.4 (C-1′), 83.1 (C-2), 82.2 (C-3), 80.6 (C-4), 79.6 (C-4′), 72.6 (C-2′), 70.6 (C-3′), 64.1 (CH_2OBz), 62.9 (C-5′), 26.6 and 24.8 ppm (2 CH_3); HRCIMS *m*/*z* obsd 823.2173 calcd for $C_{43}H_{39}N_2O_{13}S$ 823.2173.