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Reactivity of 2-Deoxy-2-iodoglycosyl Isothiocyanates with O-, S-, and N-Nucleophiles. Synthesis of Glycopyranoso-Fused Thiazoles

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Abstract: The reactivity of 2-deoxy-2-iodoglycosyl isothiocyanates toward O- and S-nucleophiles gives an easy access to 2-deoxy-2-iodoglycopyranosyl thiocarbamates and dithiocarbamates. Internal nucleophilic displacement of the iodine by the sulfur atom in these compounds allows the preparation of glycopyranoso[1,2-*d*]-1,3-thiazoles and glycopyranoso-[1,2-*d*]-1,3-thiazolidin-2-one or -2-thione. Reaction with amines or polyamines as N-nucleophiles led directly to 2-aminoglycopyranoso[1,2-*d*]-1,3-thiazoles without isolation of the intermediate thioureas. Methyl 2-deoxy-2-iodoglycopyranosyl thiocarbamates also allow the synthesis of 2-deoxyglycopyranosyl thiocarbamates or 2-deoxy-2-iodoglycopyranosyl carbamates.

Sugar isothiocyanates are among the most versatile synthetic intermediates in carbohydrate chemistry. They play a pivotal role in the preparation of a broad series of functional groups such as amide, isonitrile, carbodiimide, and *N*-thiocarbonyl derivatives allowing, simultaneously, the covalent coupling of a quite unrestricted variety of structures to the saccharide part.[1−3] Moreover, isothiocyanates are important reagents in heterocyclic chemistry, which may be exploited in the synthesis of nucleosides and other N-glycosyl structures.[4−7] We have contributed to this field[8] with the development of a convenient methodology for the simultaneous introduction of the iodo and isothiocyanate functionalities in a sugar molecule starting from glycals. Thus, electrophilic addition of iodine(I) thiocyanate, generated in situ from silica-supported KSCN and iodine, to the double bond leads exclusively to *trans*-2-deoxy-2-iodoglycopyranosyl isothiocyanates. These compounds are β-iodoalkyl isothiocyanates which constitute useful and versatile tools in the synthesis of heterocycles.[9]

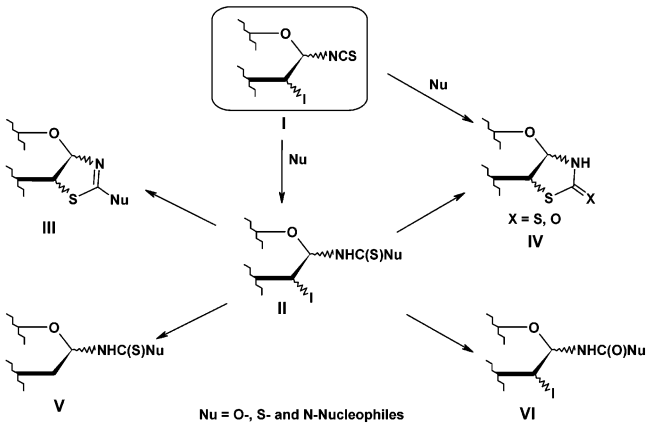

FIGURE 1.

The simultaneous presence of two active electrophilic groups in 2-deoxy-2-iodoglycosyl isothiocyanates (type I compounds, Figure 1) enhance the reactivity of these compounds emerging as valuable starting materials. Thus, it could be anticipated that nucleophilic addition to the isothiocyanate group of O-, S-, and N-nucleophiles should give an easy access to 2-deoxy-2-iodoglycopyranosyl thiocarbamates, dithiocarbamates, and thioureas (type II compounds, Figure 1). Moreover, it could be expected that the sulfur atom in these compounds produces the internal nucleophilic displacement of the vicinal iodine atom allowing the preparation of glycopyranoso[1,2-*d*]-1,3-thiazoles (type III compounds, Figure 1) and glycopyranoso[1,2-*d*]-1,3-thiazolidin-2-one or -2-thione (type IV compounds, Figure 1). The functionality of compounds of type II can be additionally exploited for the synthesis of 2-deoxyglycopyranosyl thiocarbamates (type V compounds, Figure 1) through a reductive dehalogenation or by transformation into the corresponding carbamates (type VI compounds, Figure 1). In this paper, we report the results obtained in the experimental evaluation of these hypotheses and, as a consequence, the implementation of an easy access to a wide variety of 1,3-thiazole-fused carbohydrates.

As previously described by us,[8] the monosaccharidic and disaccharidic 2-iodoglycopyranosylisothiocianates **1**−**4** were obtained from the corresponding glycals. We first investigated the reactions of these compounds with O- and S-nucleophiles. Thus, the reactions of **1**−**4** with MeOH were performed at room temperature in 1,2-dichloromethane yielding the corresponding thiocarbamates **5** and **7**−**9** in high yield (75−87%) (see Table 1, entries 1 and 3−5, respectively). Reaction with S-nucleophiles was only carried out in the case of compound **1** using ethanethiol as nucleophile, and by this way the dithiocarbamate **6** was isolated in 95% yield (see Table 1, entry 2). It should be also mentioned that the reaction of **1** with higher alcohols (ethanol, propan-2-ol, 1,2.3,4-di-*O*-isopropylidene-α-D-galactopyranose) failed in all

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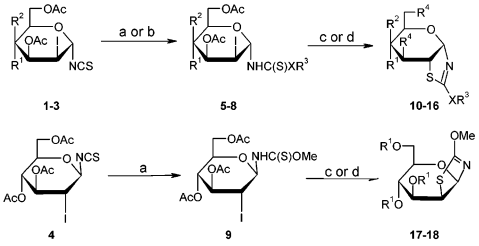
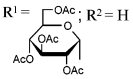
TABLE 1. Synthesis of *N*-(2-Deoxy-2-iodo-glycopyranosyl)thio or Dithiocarbamates and 2-Methoxy- or 2-Ethylthio-4,5-dihydro-1,2-dideoxy-glycopyranoso[1,2-*d*]-1,3-thiazoles[a]



Entry	Starting Material	Reaction Conditions[c]	Compound	Yield (%)
1	**1** R^1 = OAc, R^2 = H	a	**5** R^1 = OAc, R^2 = H; R^3 = Me; X = O	75
2	**1**	b	**6** R^1 = OAc, R^2 = H; R^1 = Et; X = S	95
3	**2** R^1 = H, R^2 = OAc	a	**7** R^1 = H, R^2 = OAc; R^3 = Me; X = O	86
4	**3** R^1 =  ; R^2 = H	a	**8** R^1 =  ; R^2 = H; R^3 = Me; X =O	87
5	**4**	a	**9**	87
6	**5**	c	**10** R^1 = R^4 = OAc, R^2= H; R^3 = Me; X = O	66
7	**5**	d	**11** R^1 = R^4 = OH, R^2 = H; R^3 = Me; X = O	95
8	**6**	c	**12** R^1 = R^4 = OAc, R^R = H; R^3 = Et; X = S	62
9	**7**	c	**13** R^1 = H; R^2 = R^4 = OAc,; R^3 = Me; X = O	71
10	**7**	d	**14** R^1 = H; R^2 = R^4 = OH,; R^3 = Me; X = O	89
11	**8**	c	**15** R^1 =  ; R^2 = H; R^3 = Me; R^4 = OAc; X =O	65
12	**8**	d	**16** R^1 =  ; R^2 = H; R^3 = Me; R^4 = OH; X =O	94
13	**9**	c	**17** R^1 = OAc	65
14	**9**	d	**18** R^1 = OH	50

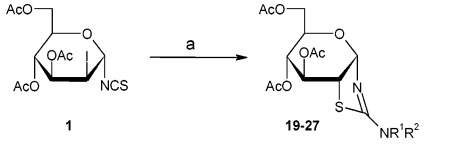
[a] Reaction conditions: (a) MeOH, 1,2-dichloroethane, reflux; (b) EtSH, Et_3N, 1,2-dichloroethane, 0 °C; (c) DBU−C_6H_6; (d) NaOMe/MeOH.

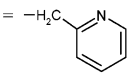
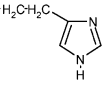
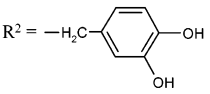
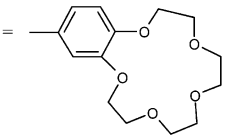
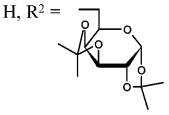
cases. This behavior can be attributed to the weaker nucleophicity as well as to higher steric requirements of these reagents.

The presence of a good leaving group vicinal to the thiocarbamate or dithiocarbamate functionality in **5**−**9** made these compounds attractive substrates for reactions based on neighboring-group participation. Such processes have been reported[10] in analogous thioureido, thiourethano, and dithiocarbamoyl derivatives of sugars with a *trans*-diaxial relationship where spontaneous cyclizations have always been observed. The outcome of the reaction has been demonstrated to be dependent on the particular reaction conditions used. Thus, aziridine formation by participation of nitrogen occurs under conditions sufficiently basic to convert the neighboring group into its anionic form. Alternatively, participation of the sulfur atom is observed when less basic conditions are used leading to the corresponding five-membered fused heterocycles (type III compounds, Figure 1). We select DBU and NaOMe−MeOH as bases to perform such processes in compounds **5**−**9**. From these reactions, formation of the 4,5-dihydroglycopyranoso[1,2-*d*]1,3-thiazoles **10**−**18** is accounted as the only detectable process (Table 1), and in each case the corresponding epimines were isolated.

(10) Goodman, L. *Adv. Carbohydr. Chem.* **1967**, *22*, 109−175.

TABLE 2. Synthesis of 2-Alkylamino-4,5-dihydro-1,2-dideoxyglycopyranoso[1,2-*d*]-1,3-thiazole[a]



Entry	Compound	Yield (%)
1	**19** R^1 = H, R^2 = CH_2Ph	54
2	**20** R^1 = H, R^2 = CH_2CH_2OH	92
3	**21** R^1 = R^2 = CH_2CH_2OH	59
4	**22** R^1 = H, R^2 = $CH_2C(O)OMe$	75
5	**23** R^1 = H, R^2 = 	79
6	**24** R^1 = H, R^2 = 	100
7	**25** R^1 = H, R^2 = 	96
8	**26** R^1 = H, R^2 = 	92
9	**27** R^1 = H, R^2 = 	77

[a] Reagent and conditions: (a) (i) HNR^1R^2, THF, rt, (ii) Et_3N.

The fused thiazolines **10**−**18** were isolated in good to high yield (50−95%).

As a next step, we investigated the behavior of 2-iodomannopyranosylisothiocyanate **1** toward N-nucleophiles. For this purpose, a variety of nitrogenated compounds were selected from primary and secondary amines with different degrees of complexity. The selection of the nucleophiles was based on structural criteria regarding the elucidation of basic aspects of the process as well potential application of the resulting compounds. Until now, the synthesis of glycopyranoso[2,1-*d*]-1,3-thiazolines has been reported in scarce cases starting from 2-deoxy-2-thioacetamido-[11,12] or 2-deoxythioureidoglycopyranoses by intramolecular cyclization.[13,14] Application of thiazolines such as enzyme inhibitors has been proved by Knapp et al., who recently prepared 2-methyl-1,2-dihydro-α-D-glucopyranoso[2,1-*d*]-1,3-thiazole and reported its powerful inhibitory effect of *N*-acetyl-*β*-hexosaminidase.[11] We performed the reactions of **1** with the nitrogenated compounds indicated in Table 2 without isolation of the thioureas intermediates that result from the attack of

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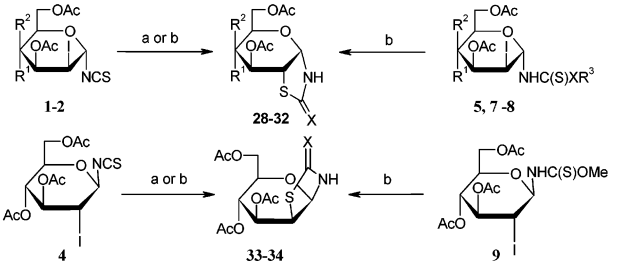
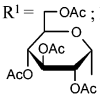
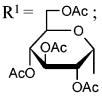
TABLE 3. Synthesis of Glycopyranoso[1,2-d]-1,3-thiazolidine-2-one and −2-thione[a]



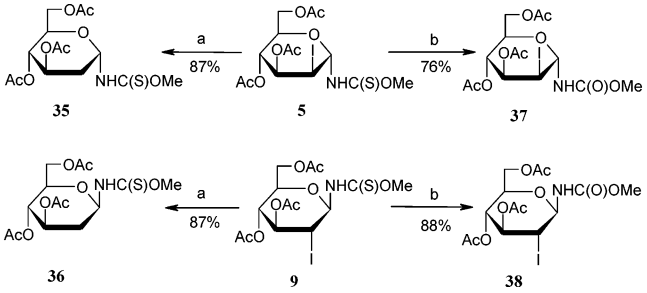
Entry	Starting Material	Reaction Conditions[a]	Compound	Yield (%)
1	**1** R^1 = OAc, R^2 = H	a	**28** R^1 = OAc, R^2 = H; X = S	38
2	**2** R^1 = H, R^2 = OAc	a	**29** R^1 = H, R^2 = OAc; X = S	85
3	**1**	b	**30** R^1 = OAc, R^2 = H; X = O	75
4	**5** R^1 = OAc, R^2 = H; R^3 = Me; X = O	b	**30**	77
5	**2**	b	**31** R^1 = H, R^2 = OAc; X = O	33
6	**7** R^1 = H, R^2 = OAc; R^3 = Me; X = O	b	**31**	38
7	**8** R^1 =  ; R^2 = H	b	**32** R^1 =  ; R^2 = H; X = O	41
8	**4**	a	**33** X = S	84
9	**4**	b	**34** X = O	87
10	**9**	b	**34** X = O	61

[a] Reaction Conditions: (a) $Na_2S·9H_2O$, acetone−water, rt; (b) MeOH, 1,2-dichloroethane, reflux

the N-nucleophiles to the isothiocyanate function. Direct treatment of such intermediates with trietylamine or DBU as bases produces the in situ internal displacement of the iodine group allowing the formation and isolation of the corresponding fused 2-amino thiazolines. Reactions with the commercially available amines benzylamine, ethanolamine, bis(2-hydroxyethyl)amine, methyl glycinate, 2-aminomethylpyridine, 4-(2-aminoethyl)-imidazole, 4,5-dihidroxybenzylamine, and 4-aminobenzo-crown-18 as well as with the amino sugar 6-amino-6-deoxy-1,2.5,6-di-*O*-isopropylidene-α-D-galactopyranose[15] were performed under the same reaction conditions using THF as solvent leading to the 2-amino thiazolines **19**−**27** in good yields (see Table 2).

We then treated 2-iodoglycopyranosylisothiocyanates **1**, **2**, and **4** with sodium sulfide in acetone. As expected, the corresponding glycopyranoso[1,2-*d*]thiazolidine-2-thiones **28**, **29**, and **33** were obtained as a consequence of the nucleophilic addition of the sulfide anion and subsequent nucleophilic displacement of the iodine atom (entries 1, 2, and 8; Table 3). Access to analogous glycopyranoso[1,2-*d*]thiazolidin-2-ones **30**−**32** and **34** is also possible from the thiocarbamates derivatives **5** and **7**−**9** (entries 4, 6, 7, and 10; Table 3) or starting directly from the 2-deoxy-2-iodoglycopyranosylisothiocyanates **1** and **2** (entries 3 and 5; Table 3) by treatment with refluxed methanol in the absence of bases. Under these conditions, the iodine ion forces the elimination of methyl iodide from the 2-methoxy glycopyranoso[1,2-*d*]-1,3-thiazoline intermediates formed (compounds **10**, **13**, **15**, and **17**) and the fused thiazolidin-2-ones are thus obtained.[9]

SCHEME 1. Synthesis of 2-deoxy-glycopyranosyl Thiocarbamates and 2-deoxy-2-iodo-Glycopyranosyl Carbamates[a]



[a] Reagents and Conditions: (a)HBu_3Sn, AIBN, ether, reflux; (b) $Hg(AcO)_2$, CH_2Cl_2, rt.

To further exploit the versatility of the 2-deoxy-2-iodo-glycopyranosylthiocarbamates (type II compounds, Figure 1) we performed the reductive dehalogenation in compounds **5** and **9**. Treatment of these compounds with tributyltin hydride in the presence of a catalytic amount of AIBN furnished the corresponding 2-deoxyglycopyranosylthiocarbamates **35** and **36**, respectively, in high yield (87%, see Scheme 1). In addition, the transformation of the thiocarbamates **5** and **9** into the corresponding carbamates **37** and **38** could be easily effected by treatment with $Hg(AcO)_2$ (76% and 78%, respectively).

The results described above prompted us to also investigate the possibility of building neoglycoconjugates bearing multiple glycopyranoso[1,2-*d*]thiazolidine moieties in a single structure. In the past, glycopyranosyl isothiocyanates have been extensively used for the preparation of a variety of neoglycoconjugates.[3] To attain this goal, we selected various symmetrical diamines (1,2-ethanediamine, 1,6-hexanediamine, 2-hydroxy-1,3-propanediamine, 25,27-bis(aminoethoxy)-5,11,17,23-tetra-*tert*-butyl-26,28-dihydroxycalix[4]arene[16]), and triamines (tris(2-aminoethyl)amine, *N*-(2-aminoethyl)-1,2-ethanediamine) and performed the reactions under the same conditions described above. The reactions of **1** with the named diamines lead to the bis-glycopyrano[1,2-*d*]thiazolines **39**−**42** in good to high yields (see Scheme 2). Similarly, the tris-glycopyrano[1,2-*d*]thiazolines **43** and **44** were easily obtained when **1** reacted respectively with tris(ethyleneamino)amine that possesses three primary amine functions or with *N*-(2-aminoethyl)-1,2-ethanediamine that bears two primary amine groups and one secondary amine function.

The structures of all the new compounds were established on the basis of the spectroscopic data. A comment is only needed in relation to the observed $^3J_{H,H}$ values for **5**−**8** and **37** that suggest that $^1C_4$ conformation for this compounds is not the preferred as expected. In compounds **5**, **6**, and **37,** the $^3J_{1,2}$ values in the range 5.5−5.8 Hz suggest a conformational equilibrium $^4C_1 \rightleftharpoons {}^1C_4$ with a preference for the $^1C_4$ conformation. However, compounds **7** and **8** show $^3J_{1,2} > 8.0$ Hz in agreement with a predominant $^1C_4$ conformation in which the bulky iodine group and the carbamate or thiocarbamate group

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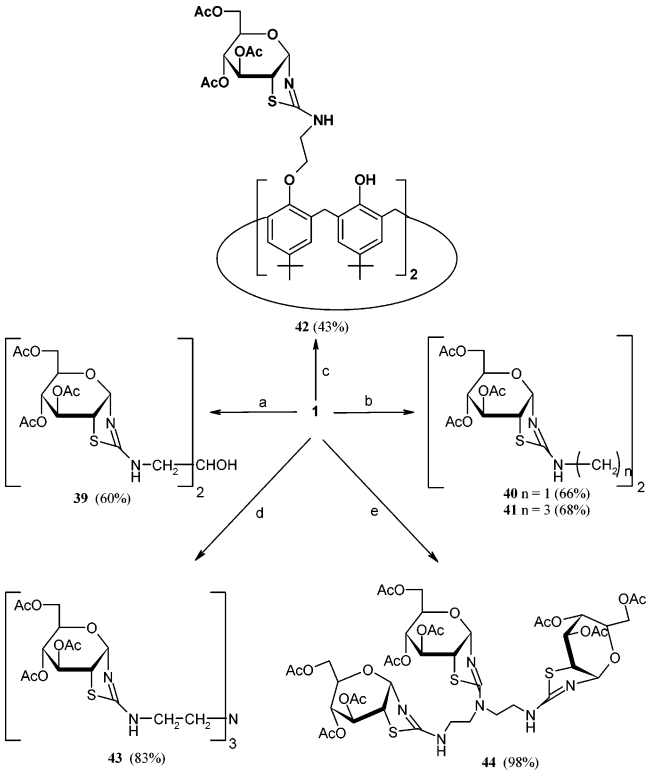
(16) Zhang, W. C.; Huang, Z. T. *Synthesis* **1997**, 1073−1076.

SCHEME 2. Synthesis of Bis- and Tris-4,5-dihydro-1,2-dideoxyglycopyranoso[1,2-d]-1,3-thiazole[a]



[a] Reagents and conditions: (a) (i) $NH_2CH_2CH(OH)CH_2NH_2$, THF, (ii) Et_3N; (b) (i) $NH_2CH_2(CH_2)_nNH_2$ (n = 1,5), THF (ii) Et_3N; (c) (i) 25,27-bis-(aminoethoxy)-5,11,17,23-tetra-*tert*-butyl-26,28-dihydroxy-calix[4]arene, THF, (ii) Et_3N; (d) (i) $N(CH_2CH_2NH_2)_3$, TFH; (ii) DBU; (e) (i) $(H_2NCH_2CH_2)_2NH$; (ii) Et_3N.

are in an equatorial disposition. Similar behavior has been observed by us[17] and others[18−20] in similar 2-deoxy-2-iodopyranosyl derivatives having an antiperiplanar substituent at the anomeric position in relation with the iodine group. Although a better understanding of the reasons that determine this conformational change is needed, steric factors can be pointed out as the main cause, supported by the fact that the $^4C_1$ conformation is observed for the 2-deoxyglycopyranosyl thiocarbamate **35** where the iodine atom at the C-2 position is absent.

In conclusion, we have demonstrated that 2-deoxy-2-iodoglycosyl isothiocyanates are versatile compounds that allow an easy access to a variety of 1,3-thiazole-fused carbohydrates as well as glycopyranoso[1,2-*d*]-1,3-thiazolidin-2-one and -2-thione by reaction with O-, S-, and N-nucleophiles. Remarkable features of this methodology are the simplicity of the experimental procedures and the fact that it allows the synthesis of these heterocyclic fused sugar derivatives in good to high yields. Application of these results has allowed the synthesis of multivalent neoglycoconjugates bearing multiple glycopyranoso[1,2-*d*]thiazolidine moieties in a single structure by reaction with poliamines as nucleophiles.

Acknowledgment. We thank Dirección General de Investigación Científica y Técnica for financial support (BQ2002-03477).

Supporting Information Available: General experimental details, full purification and characterization data, as well as ^1H and ^{13}C NMR spectra for compounds **5**−**44**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034996I

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(21) This product experiment spontaneous transformation in the corresponding 1,3-thiazole derivative **17** when dissolved in DMSO-d_6 or $CDCl_3$ at rt as indicated by ^1H NMR.