Novel glycosylidene-spiro-heterocycles from unprecedented solvent incorporation in Koenigs–Knorr-like reactions of *C*-(1-bromo-1-deoxy-β-D-glycopyranosyl)formamides

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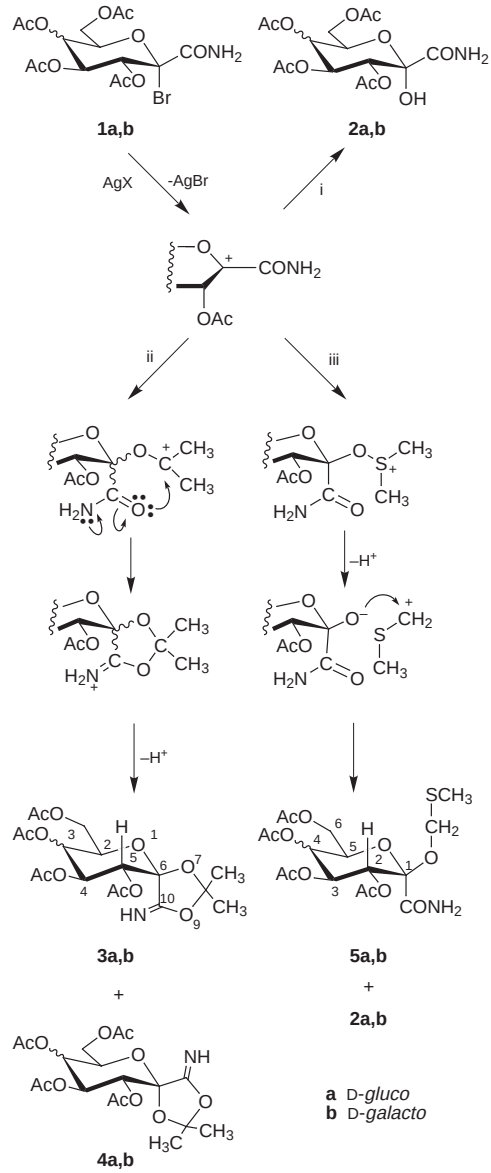
The title compounds give glycopyranosylidene-spiro-dioxolanes 3 and 4 in acetone and *C*-(1-methylsulfanylmethoxy-α-D-glycopyranosyl)formamides 5 in DMSO in the presence of Ag_2CO_3 and AgF, respectively.

As part of an ongoing program to synthesize new anomerically bifunctional monosaccharide derivatives[1–3] as glycomimetics and their precursors we have investigated the reactions of acetylated *C*-(1-bromo-1-deoxy-β-D-glycopyranosyl)formamides (**1a**[3] and **1b**[4]) with nucleophiles under Koenigs–Knorr conditions.[5] While reaction of **1a**,**b** with 1 equiv. of water in DMSO in the presence of Ag_2O (Scheme 1) gave the expected hydroxyformamide derivatives **2a**,**b** in a crystalline state[6] [**2a**: 85%, mp 177–179 °C, $[\alpha]_D$ +36 ($CHCl_3$, *c* 1.03); **2b**: 89%, mp 143–144 °C, $[\alpha]_D$ +53 ($CHCl_3$, *c* 1.0)], a similar transformation of **1b** in acetone[7] produced the spiro compound **3b** in addition to **2b** (ratio ~1:1 by ^1H NMR spectroscopy). Using dry acetone with Ag_2CO_3 gave **3a**,**b** [**3a**: 78%, mp 165–167 °C, $[\alpha]_D$ +21 ($CHCl_3$, *c* 1.0); **3b**: 71%, mp 155–157 °C, $[\alpha]_D$ +31 ($CHCl_3$, *c* 1.0)] and small amounts of **4a**,**b** [**4a**: 6%, syrup, $[\alpha]_D$ +39, ($CHCl_3$, *c* 2.06); **4b**: 4%, syrup, $[\alpha]_D$ +57, ($CHCl_3$, *c* 1.06)] and **2a**,**b** (~5% for each) after chromatographic separation. Carrying out the reaction in dry DMSO with AgF the methylsulfanylmethoxyformamides **5a**,**b** [**5a**: 11%, syrup, $[\alpha]_D$ +21 ($CHCl_3$, *c* 1.03); **5b**: 15%, mp 155–156 °C, $[\alpha]_D$ +29 ($CHCl_3$, *c* 1.07)] could be isolated as minor products over **2a**,**b**. Experiments with **2a** showed that this compound was unchanged after one day when dissolved in acetone or DMSO either in the absence or presence of Ag_2CO_3 or AgF, respectively.

Structure elucidation† of **3**–**5** was performed by NMR (Tables 1 and 2) and MS measurements. Incorporation of acetone in **3** and **4** was indicated by a molecular ion (*m/z* 431, M^+ for each) and by two methyl singlets. The presence of one exchangable proton belonging to an sp^2-hybridized nitrogen as shown by $^{15}N/^1H$ HSQC experiments, and carbon resonances indicative of an imino ether moiety (C-10) as well as for an acetal carbon (C-8) are in accordance with the cyclic stuctures. For each derivative the vicinal proton–proton couplings showed that the sugar rings existed in the $^4C_1$ conformation. The configuration of the spiro carbons was established by the three bond heteronuclear coupling between H-5 and C-10, indicating antiperiplanar arrangement for the nuclei involved in the given conformation (see Scheme 1). This was corroborated by the characteristic downfield shifts of the sugar protons *cis* to C-10 (H-2 and H-4 in **3a**,**b**, H-5 in **4a**,**b**) following a rule established recently for glycopyranosylidene-spiro-hydantoin derivatives.[2] This effect, which is a further indirect proof of the spirocyclic structure, is attributed to the shielding anisotropy contribution of the C=NH bond which occupies a fixed position with respect to the sugar ring.

Compounds **5** had a fragment ion (*m/z* 407, $[M - CONH_2]^+$ for each) and characteristic resonances for a $CONH_2$ group and a OCH_2SCH_3 moiety. The anomeric configurations followed from the $^3J_{H\text{-}2,CONH_2}$ couplings indicating the *trans*-diaxial relationship of the two nuclei in the $^4C_1$ conformation.

Based on the experimental data available at present we think that formation of these derivatives of novel structure can most probably be explained by participation of the solvents used. The first step probably common for each transformation may be the generation of a glycosylium ion destabilized by the electron-withdrawing $CONH_2$ substituent. This intermediate can com-



Scheme 1 *Reagents and conditions*: i, AgX = Ag_2O (1 equiv.), DMSO, H_2O (1 equiv.), 3 h, room temp.; ii, AgX = Ag_2CO_3 (1 equiv.), dry acetone, 18 h, room temp., N_2; iii, AgX = AgF (1.5 equiv.), dry DMSO, 0.5 h, room temp.

Table 1 Selected NMR data for **3** and **4** (δ/ppm, J/Hz)

	3a	**3b**	**4a**	**4b**
CH_3	1.48, 1.61	1.49, 1.69	1.61, 1.63	1.59, 1.63
CH_3	27.55, 26.91	27.63, 26.90	27.40, 26.65	27.49, 26.74
=N*H*	197.0	198.7	[a]	[a]
=N*H*	7.51	7.42	7.42	7.41
C-8	112.70	112.56	112.60	112.46
C-10	160.10	160.27	160.90	161.21
$^3J_{H\text{-}5,C\text{-}10}$	5.4	5.6	[a]	[a]
H-2 ($J_{2,3}$)	4.65 (10.2)	4.88 (1.1)	4.20 (9.5)	4.41 (1.4)
H-4 ($J_{3,4}$)	6.08 (9.8)	6.00 (3.3)	5.40 (9.0)	5.25 (3.3)
H-5 ($J_{4,5}$)	5.33 (10.2)	5.58 (10.8)	5.53 (9.8)	5.74 (11.0)

[a] Not measured because of insufficient sample quantity.

Table 2 Selected NMR data for **5**

	5a		**5b**	
	^{1}H	^{13}C	^{1}H	^{13}C
–OCH_2S–	4.78, 4.72	67.95	4.93, 4.84	67.88
–SCH_3	2.11	14.82	2.11	14.91
$CONH_2$	6.71, 5.98	168.76	6.69, 5.69	169.21
H-2 ($J_{2,3}$)	5.23 (9.0)	—	5.40 (10.6)	—
H-4 ($J_{3,4}$)	5.82 (9.0)	—	5.82 (3.2)	—
H-5 ($J_{4,5}$)	5.16 (10.0)	—	5.47 (1.4)	—
$^3J_{H\text{-}2,CONH_2}$	—	4.6	—	4.9

bine with a nucleophilic molecule present in the reaction mixture, *i.e.* water, acetone or DMSO. While deprotonation of the species obtained after combination of the glycosylium ion with a water molecule leads to the stable molecule **2**, the alkoxydimethylsulfonium intermediate (from combination with DMSO) may be deprotonated at one of the methyl groups to give **5** after a Pummerer-type rearrangement.[8] The intermediate (from combination with acetone) may be stabilized by an attack of the oxygen of the $CONH_2$ group at the positively charged carbon. The cyclic structure formed in this step can be deprotonated at the iminium moiety to result in the spirocyclic compounds **3** and **4**.

To the best of our knowledge similar solvent participation and incorporation is only known with some nitriles (mainly acetonitrile) in the sugar series.[9,10] These new, simple reactions provide ready access to novel glycopyranosylidene-spiro-heterocycles **3** and **4** that can be regarded as analogues of sugar spiro-hydantoin derivatives with important biological effects (see references in ref. 2) as well as to compounds of type **5** that can be useful orthogonally protected synthetic intermediates. The scope and limitations of the reported transformations are currently being investigated in our laboratory.

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Notes and references

† Each new compound gave satisfactory elemental analysis. The NMR spectra were recorded for $CDCl_3$ solutions with reference to internal TMS in the ^{1}H, to the solvent signal in the ^{13}C, and to external NH_4Cl in the ^{15}N NMR experiments. MS: EI 70 eV.

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