2-Amino-2-deoxyglycoside Derivatives via Hofmann Rearrangement of 2-Carbamoyl-2-deoxyglycosides

Danuta Mostowicz, Czesław Bełżecki, Marek Chmielewski*
Institute of Organic Chemistry, Polish Academy of Sciences, P-01-224 Warsaw, Poland

Methyl 2-methoxy- and 2-*tert*-butoxycarbonylamino-2-deoxyglycosides were obtained from methyl 2-carbamoyl-2-deoxyglycosides via Hofmann rearrangement with sodium methoxide/bromine/methanol or sodium hydroxide/sodium bromite/methanol or lead tetraacetate *tert*-butyl alcohol/dimethylformamide.

The vinyl ether grouping present in glycals determines the regiospecificity of the addition or cycloaddition reactions which can take place at the double bond. As a consequence of the frontier electron population of that function,[1] the elecrophilic portion of the entering molecule is added to C-2 of a glycal whereas the nucleophilic portion is added to the anomeric carbon. This regiochemistry has been utilized in many reactions leading to 2-amino-2-deoxy sugars.[2]

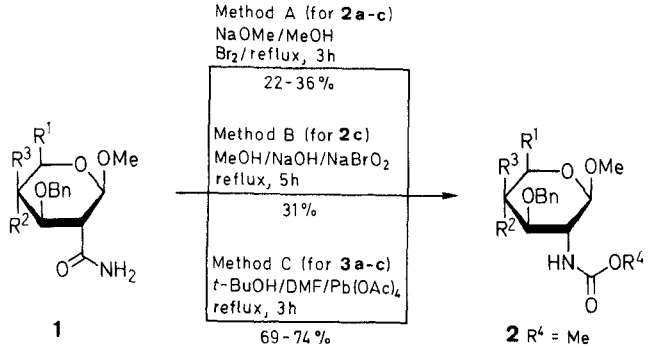
Recently we have reported a two-step methoxycarbamoylation of glycals, involving isocyanate cycloaddition followed by opening of the resulting azetidinone ring with methanol.[3] The regio- and stereospecificity of this process offers new attractive possibilities for formation of 2-amino-2-deoxy sugars via Hofmann rearrangement of the carbamoyl group. We have used this reaction with three representative methyl glycosides with the β-D-gluco **1a**, β-D-galacto **1b**, and the α-L-arabino configuration **1c**, obtained from the respective benzylated glycals.[4]

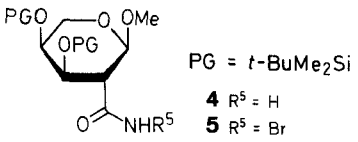
Treatment of **1** with bromine in the presence of sodium methoxide produces, under standard conditions[5] carbamates **2** in only 22–36% yield (Table). The intermediate 2-bromoamide, which is formed as the primary product in the course of the reaction, slowly undergoes Hofmann rearrangement or reduction to the substrate. The similar rates of both reactions are the cause of the low yield of the rearrangement; chromatographic separation of the crude product affords about 30% of the substrate. In the case of the α-L-arabino glycoside **4**, with *tert*-butyldimethylsilyl protecting groups, the 2-bromoamide **5** is stable enough to be isolated.[6]

The yield of Hofmann rearrangement (31%) was also low when amide **1c** was treated with sodium bromite in the presence of sodium hydroxide in methanol.[7]

Hofmann rearrangement of compounds **1** was also effected with lead tetraacetate in *tert*-butyl alcohol/dimethylformamide.[8] With 5 equivalents of lead tetraacetate, the reaction proceeded smoothly to give the carbamates **3** in 69–74% yield (Table).

We have shown that methoxycarbamoylation of glycals, followed by Hofmann rearrangement of the carbamoyl function, offers a new interesting method for formation of 2-amino-2-deoxy sugars.





1–3	R^1	R^2	R^3
a	CH_2OBn	OBn	H
b	CH_2OBn	H	OBn
c	H	H	OBn

All reagents were of commercial quality. $Pb(OAc)_4$ and $NaBrO_2$ were purchased from Fluka Chemical Co. Solvents were dried and purified by standard methods. Analytical TLC was performed on aluminum sheets coated with a 0.2 mm layer of silica gel 60 F_{254}, Merck. Silica gel 60 (70–230 mesh), Merck, was used for column chromatography. Melting points were taken using a Kofler apparatus (MLW, GDR) and are uncorrected. Microanalyses were obtained using a Perkin-Elmer M-240 element analyser. Optical rotations were measured with a Perkin-Elmer 141 spectropolarimeter. IR spectra were recorded with a Beckman 4240 spectrophotometer. ^{1}H-NMR spectra were performed on a Bruker AM 500 (500 MHz) instrument.

Methyl 2-Deoxy-2-(methoxycarbonylamino)pyranosides 2; General Procedures:

Method A: (for **2a–c**): To a stirred solution of **1a–c** (1.0 mmol) in abs. MeOH (10 mL) is added NaOMe (0.108 g, 2.0 mmol) in MeOH (5 mL), followed by Br_2 (0.05 mL, 1.0 mmol). The solution is stirred and refluxed for 3 h. Subsequently the mixture is cooled and treated with AcOH (0.3 ml). The solvent is removed *in vacuo*, and the residue is treated with $CHCl_3$ (25 mL) and H_2O (5 mL). The organic layer is separated, washed with brine (5 mL), and dried ($MgSO_4$). The solvent is removed *in vacuo* and the residue is chromatographed on a silica gel column (15 × 2 cm) using hexane/Et_2O/MeOH (10:10:0.5) as an eluant to afford **2** and unreacted **1**.

Method B: (for **2c**): Glycoside **1c** (0.37 g, 1.0 mmol) is dissolved in abs. MeOH (10 mL), and treated wtih NaOH (0.135 g, 3.3 mmol) and $NaBrO_2$ (0.094 g, 6.6 mmol). The solution is stirred and refluxed for 5 h. Subsequently the mixture is cooled and treated with AcOH (0.5 mL). Workup as described above gives unreacted **1c** (6%) and the glycosides **2c**; yield: 0.12 g (31%);

Methyl 2-(*tert*-Butoxycarbonylamino)-2-deoxypyranosides 3; General Procedure:

Method C: (for **3a–c**): Glycoside **1a–c** (0.5 mmol) is dissolved in a mixture of *t*-BuOH (10 mL) and DMF (5 mL). Subsequently $Pb(OAc)_4$ (1.1 g, 2.5 mmol) is added and the mixture is stirred and refluxed for 3 h. Solvents are removed *in vacuo*, and the residue is chromatographed on a silica gel column (10 × 2 cm) using hexane/Et_2O (7:3) as an eluant to give **3a–c**.

Table. Hofmann Rearrangement of Methyl 2-Carbamoyl-2-deoxyglycosides **1a–c**

Substrate	Product	Method	Yield[a] (%)	mp (°C)[b] (solvent)	$[\alpha]_D$ (*c*, $CHCl_3$)	Molecular Formula[c]	IR ν (cm^{-1})	^{1}H-NMR (solvent/TMS, 500 MHz)[d] δ, *J* (Hz)
1a	**2a**	A	36 (30)	138–139 (EtOAc/Hx)	+16.5 (0.6)	$C_{30}H_{35}NO_7$ (521.5)	1710	(C_6D_6, 70 °C): 3.29 (s, 3H, OCH_3), 3.42 (s, 3H, $OCOCH_3$), 3.49 (dt, 1H, J_{45} = 9.3, J_{56} + $J_{56'}$ = 7.2, H-5), 3.54 (dd, 1H, J_{34} = 8.4, H-4), 3.64 (t, 1H, J_{23} = 9.0, H-3), 3.71 (m, 2H, H-6,6'), 3.84 (br t, 1H, J_{12} = 8.3, H-2), 4.44 (br d, 1H, H-1)
1b	**2b**	A	33 (31)	161–163 (EtOAc/Hx)	+25.7 (1.0)	$C_{30}H_{35}NO_7$ (521.5)	1710	(C_6D_6, 70 °C): 3.34 (s, 3H, OCH_3), 3.39 (s, 3H, $OCOCH_3$), 3.56 (br t, 1H, H-5), 3.64 (dd, 1H, J_{56} = 5.5, $J_{66'}$ = 9.2, H-6), 3.78 (br q, 1H, H-2), 3.79 (dd, 1H, $J_{56'}$ = 7.4, H-6'), 3.90 (br d, 1H, $J_{34} \approx$ 2.3, H-4), 3.94 (br d, 1H, J_{23} = 9.9, H-3), 4.65 (br d, 1H, J_{12} = 8.0, H-1)
1c	**2c**	A	22 (29)	180–181 (EtOAc/Hx)	+21.3 (0.9)	$C_{22}H_{27}NO_6$ (401.5)	1710	(C_5D_5N, 100 °C): 3.43 (s, 3H, OCH_3), 3.50 (dd, 1H, J_{45} = 2.2, $J_{55'}$ = 12.1, H-5), 3.63 (s, 3H, $OCOCH_3$), 3.95 (m, 1H, H-4), 4.10 (dd, 1H, J_{23} = 8.7, J_{34} = 3.2, H-3), 4.22 (dd, 1H, $J_{45'}$ = 4.5, H-5'), 4.33 (dt, 1H, J_{12} = 6.3, H-2), 4.72 (d, 1H, H-1)
		B	31					
1a	**3a**	C	73	143–144 (benzene/Hx)	+14.2 (1.0)	$C_{33}H_{41}NO_7$ (563.7)	1705	(C_6D_6, 70 °C): 3.34 (s, 3H, OCH_3), 3.47 (dd, 1H, J_{34} = 8.3, J_{45} = 9.1, H-4), 3.50 (ddd, 1H, J_{56} = 4.4, $J_{56'}$ = 3.0, H-5), 3.63 (dd, 1H, J_{23} = 9.1, H-3), 3.70 (dd, 1H, $J_{66'}$ = 10.9, H-6), 3.72 (dd, 1H, H-6'), 3.89 (br t, 1H, $J_{12} \approx$ 8.0, H-2), 4.36 (br d, 1H, H-1)
1b	**3b**	C	69	159–161 (benzene/Hx)	+13.5 (1.0)	$C_{33}H_{41}NO_7$ (563.7)	1710	(C_6D_6, 70 °C): 1.4 (s, 9H, $C(CH_3)_3$, 3.36 (s, 3H, OCH_3), 3.57 (m, 1H, H-5), 3.64 (dd, 1H, J_{56} = 5.6, $J_{66'}$ = 9.2, H-6), 3.78 (m, 1H, H-2), 3.79 (dd, 1H, $J_{5'6}$ = 7.3, H-6'), 3.88 (m, 1H, H-4), 3.96 (br d, 1H, H-3), 4.65 (br d, 1H, $J_{12} \approx$ 7.5, H-1)
1c	**3c**	C	74	181–182 (benzene/Hx)	+8.8 (1.0)	$C_{25}H_{33}NO_6$ (443.5)	1705	(C_6D_6, 70 °C): 1.42 (s, 9H, $C(CH_3)_3$), 3.17 (dd, 1H, J_{45} = 2.5, $J_{55'}$ = 11.8, H-5), 3.26 (s, 3H, OCH_3), 3.42 (m, 1H, $J_{45'}$ = 5.5, J_{34} = 3.1, H-4), 3.95 (br m, 1H, H-3), 3.98 (dt, 1H, J_{12} = 5.1, J_{23} = 7.8, H-2), 4.00 (dd, 1H, H-5'), 4.50 (br d, 1H, H-1)

[a] Yield of isolated product. Yield of recovered substrate shown in parenthesis.
[b] Hx = hexane.
[c] Satisfactory microanalyses obtained: C ±0.17, H ±14, N ±0.13.
[d] Selected ^{1}H-NMR data only.

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