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ARTICLE TYPE

Novel stereocontrolled amidoglycosylation of alcohols with acetylated glycals and sulfamate ester

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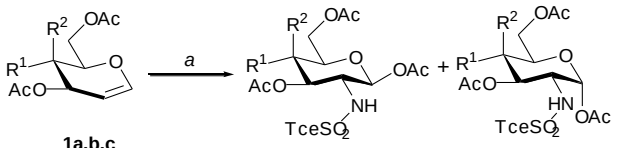
A regio- and stereo-controlled, one-pot amidoglycosylation of alcohols has been achieved using *O*-acetylated glycals, trichloroethoxysulfonamide, and iodosobenzene in the presence of a rhodium(II) catalyst. The reaction would proceed via stereoselective intermolecular aziridination of the glycal.

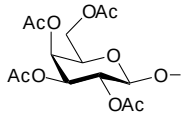
2-*N*-Acetamido-2-deoxyglycosides, most commonly of the D-glucose and D-galactose series, are widely distributed in living organisms as glycoconjugates (glycolipids, glycoproteins) and glycosaminoglycans. Aminosugars on cell surfaces are assumed to play an important role as receptor ligands for protein molecules such as enzymes, antibodies, and lectins. Except D-glucosamine, most aminosugars, *e.g.*, D-galactosamine, D-mannosamine, disaccharide lactosamine, are rather expensive as starting materials for the chemical synthesis of glycoconjugates and oligosaccharides.

Glycals (1,2-dehydro-sugar derivatives) have proved to be useful synthetic precursors of 2-amino-2-deoxy-*O*-glycosides by way of *N*-functionalisation at C-2 accompanied by addition of alcohols to C-1 (aza-glycosylation), and a variety of methods have been developed for the nitrogen transfer to glycals over the last few decades.[1] Among them, azido-nitration reactions developed by Lemieux and co-workers[2] have been widely used since the reaction of *O*-protected glycals with sodium azide and cerium(IV) ammonium nitrate provides 2-azido-2-deoxy-1-*O*-nitro-glycoses regioselectively. However, the stereoselectivities are dependent on the structure of the glycal substrate; the azidonitrations of acetylated glucal derivatives often proceed non-stereoselectively to give both epimers of the azido group at C-2 (*gluco*-*N* and *manno*-*N* isomers).[2,3]

In recent years, transition metal-catalysed inter- and intra-molecular aziridinations of alkenes have been developed by using nitrenes as a nitrogen source.[4] The highly reactive nitrene species are generated *in situ* from several types of precursors, *e.g.*, sulfonyliminoiodinanes,[5] sulfonamides[6]/sufamate esters[7]/carbamate esters[8] with iodine(III) compounds, *N*-(sulfonyloxy)carbamates with base,[9] chloramine-T,[10] and azido-compounds.[11] When the aziridination reactions are applied to glycal derivatives, the corresponding 1,2-aziridines would be formed. The anomeric C-1 position of *N*-sulfonyl or *N*-carbonyl 1,2-aziridino-glycosides would be highly electrophilic to react readily with nucleophiles providing 2-amino-2-deoxy-glycoside derivatives. There have been several reports on such aminoglycosylation reactions via aziridine intermediates.[4c] Rojas and co-workers reported intramolecular aziridinations of 3-*O*-azidoformyl-[12a] and 3-*O*-carbamoyl-D-allal derivatives[12b] and subsequent reactions with alcohols to access 2-amino-2-deoxy-β-D-allopyranosides stereoselectively. Liu and co-workers reported stereoselective synthesis of glucosamine derivatives via rhodium-catalysed, substrate-controlled aziridination of 4-*O*- or 6-*O*-sulfamoyl-D-glucal derivatives.[13] However, these precedents require preparation of the appropriate substrates for *intramolecular* aziridinations. Stereoselective synthesis of 2-amino-2-deoxy-1-*O*-glycosides from glycals via *intermolecular* aziridination[14] should be more challenging since it would likely afford a mixture of stereoisomers. Indeed, to our knowledge, this type of glycosylation has been reported only by Descotes' group; addition of photochemically generated *N*-ethoxycarbonyl-nitrenes to acetylated glycals in methanol gave the methyl 2-amino-glycosides as a mixture of three stereoisomers.[15]

Table 1 Amidoacetoxylation of acetylated glycals **1a,b,c**



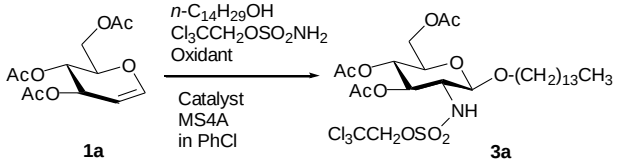
1	Yield (%) 2-β	2-α
a: R^1 = AcO, R^2 = H	91[b]	0
b: R^1 = H, R^2 = AcO	33[b]	61[b]
c: R^1 =  , R^2 = H	84[c]	8[c]

[a] Reagents and conditions: $Cl_3CCH_2OSO_2NH_2$ (1.8 equiv.), $PhI(OAc)_2$ (1.8 equiv.), $Rh_2(NHCOCF_3)_4$ (0.1 equiv.), MgO (4 equiv.) in PhCl, 5 °C, 2 h to rt, 10 h. [b] Isolated yield by silica gel chromatography. [c] The yields were determined by ^{1}H-NMR integration of the α/β mixture.

We report here a regio- and stereo-controlled amidoglycosylation of alcohols via intermolecular aziridination in a one-pot manner using simple *O*-acetylated glycals (D-glucal, D-galactal, D-lactal), which are readily prepared in 3 steps from the parent sugars. In their research on rhodium-catalysed olefin aziridination with $PhI(OAc)_2$ and sulfamate esters, Du Bois and co-workers found a stereospecific amido-acetoxylation of tri-*O*-

acetyl-D-glucal **1a** to give 2-deoxy-2-(trichloroethoxysulfonyl)amino-glucopyranosyl 1β-*O*-acetate **2a**-β in a regiospecific manner in high yield,[16] though they have not described the reaction in detail. We were interested in the amido-acetoxylation, and confirmed that the reaction of **1a** with $Cl_3CCH_2OSO_2NH_2$, $PhI(OAc)_2$, MgO in the presence of a Rh(II) catalyst [$Rh_2(NHCOCF_3)_4$] afforded the β-acetate **2a**-β only. The amidoacetoxylation was applied to acetyl-protected galactal **1b** and lactal **1c** under identical conditions. As shown in Table 1, Ac-galactal **1b** gave a 2:1 mixture of the α- and β-acetates, whereas Ac-lactal **1c** gave the β-acetate **2c**-β predominantly. In all cases, the stereoisomers at C-2 were not detected.

Table 2 Amidoglycosylation of tetradecanol with acetylated glucal **1a** and trichloroethoxysulfonamide



1a **3a**

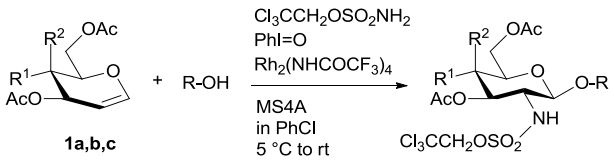
Entry	Equiv. of $C_{14}H_{29}OH$	Oxidant[a]	Catalyst	**3a** Yield (%)[b]
1[c]	4	$PhI(OAc)_2$	$Rh_2(NHCOCF_3)_4$	58[d]
2	4	PhI=O	$Rh_2(NHCOCF_3)_4$	66
3	2	PhI=O	$Rh_2(NHCOCF_3)_4$	78
4	4	PhI=O	$Rh_2(OAc)_4$	45
5	2	PhI=O	$Cu(CH_3CN)_4PF_6$	17
6	2	PhI=O	$AgNO_3$, tBu_3tpy[e]	25

[a] The oxidant (solid, 1.8 equiv.) was added in *ca*. 6 portions to the mixture of other reactants for *ca*. 1 h at 5 °C. [b] Isolated yield by silica gel chromatography. In all cases, unreacted **1a** remained. [c] MgO (4 equiv.) was used in place of MS4A. [d] 1-Acetate **2a**-β was obtained in 22% yield. [e] tBu_3tpy: 4,4',4"-tri-*tert*-butyl-2,2':6',2"-terpyridine

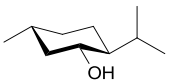
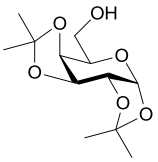
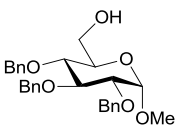
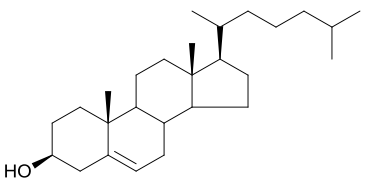
We next examined a direct synthesis of 2-sulfonamido-1-*O*-glycosides[17] from glycals by adding alcohols in the reaction mixture. As shown in Table 2, the reaction of **1a** and tetradecanol (4 equiv.)[12] with $Cl_3CCH_2OSO_2NH_2$ in the presence of $PhI(OAc)_2$ and catalytic $Rh_2(NHCOCF_3)_4$ in chlorobenzene afforded the desired tetradecyl-β-glucoside **3a** in 58% yield with no α-glucoside. However, the 1-*O*-acetate **2a**-β was also formed (entry 1). Formation of **2a** was suppressed by using iodosobenzene with 4Å molecular sieves (as dehydration agent) in place of $PhI(OAc)_2$ with MgO (entry 2). Reduction of the amount of alcohol improved the yield of **3a** (entry 3). For the aziridination catalyst, $Rh_2(OAc)_4$ was less effective than $Rh_2(NHCOCF_3)_4$, and copper(I)[6a] and silver[18] catalysts were much less effective (entries 4-6).

With the optimised reaction conditions in hand, we investigated the scope and generality of this Rh-catalysed one-pot amidoglycosylation, and the results are summarized in Table 3. Reactions of 12-bromododecanol and 2-phenylethanol with the glycals **1a**,**b**,**c** proceeded smoothly to afford the corresponding β-glycosides **4a**,**b**,**c**, **6a** in good yields (entries 1,2,3,5). In contrast, 12-acetylthio-1-dodecanol gave the galactoside **5b** in poor yield under identical conditions, indicating that the acetylthio group would suppress the reaction (entry 4). Reaction of **1b** with 4-penten-1-ol gave the β-galactoside **8b** in somewhat lower yield along with a byproduct[‡] derived from 4-pentenol, indicating that pentenol was also aziridinated, but would be less reactive than **1b** (entry 7).

Table 3 Amidoglycosylation of alcohols with acetylated glycal **1a**,**b**,**c** and trichloroethoxysulfonamide [a]



1a,b,c

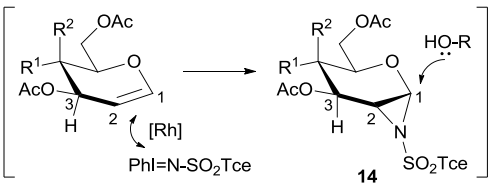
Entry	Glycal	R-OH	Product	Yield (%)[b]
1	**1a**	$Br(CH_2)_{12}$-OH	**4a**	77
2	**1b**	$Br(CH_2)_{12}$-OH	**4b**	84
3	**1c**	$Br(CH_2)_{12}$-OH	**4c**	70
4	**1b**	$AcS(CH_2)_{12}$-OH	**5b**	11
5	**1a**	$Ph(CH_2)_2$-OH	**6a**	75
6	**1b**	$PhCH_2$-OH	**7b**	62
7	**1b**	H_2C=CH-$(CH_2)_3$-OH	**8b**	63
8	**1a**	cyclohexanol	**9a**	57
9	**1b**	cyclohexanol	**9b**	78
10	**1a**	 L(-)-menthol	**10a**	74
11	**1b**	L(-)-menthol	**10b**	76
12	**1c**	L(-)-menthol	**10c**	67
13	**1b**		**11b**	74
14	**1b**		**12b**	21
15	**1b**	 cholesterol	**13b**	56

[a] General procedure: To a mixture of glycal **1**, ROH (2 equiv.), $Cl_3CCH_2OSO_2NH_2$ (1.7 equiv.), $Rh_2(NHCOCF_3)_4$ (0.1 equiv.), molecular sieves 4Å (0.8 g/mmol) in PhCl (**1**: 0.05-0.10 M) under nitrogen at 5 °C was added PhIO (1.8 equiv.) in several portions for 1 h, and the resulting suspension was stirred at 5 °C for 1 h and then at rt for 5-15 h. [b] Isolated yield by silica gel chromatography.

Cyclic secondary alcohols: cyclohexanol and L(-)-menthol reacted with the glycals **1a-c** to give the corresponding β-glycosides in good yields. Ac-galactal **1b** appeared to be more reactive and gave the glycosides in better yields than **1a** and **1c** (entries 8-12 and 1-3). For sugar-derived alcohols, 1,2:3,4-di-*O*-

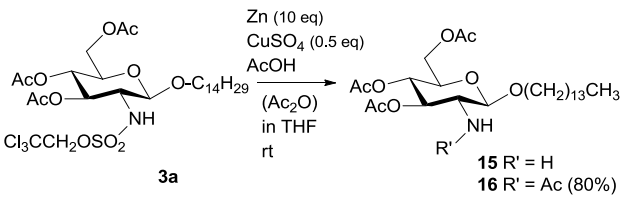
isopropylidene-α-D-galactopyranose afforded the galactoside **11b** in good yield, whereas methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside gave the galactoside **12b** in low yield, and substantial amounts of some byproducts: de-*O*-benzylated glucoses and benzaldehyde were obtained. In all the cases examined, no α-anomer was detected by ^{1}H- and ^{13}C-NMR. Small amounts (3-8%) of hydrolysed products (1-OH) were formed in most cases.

The reaction would proceed via the generation of sulfonyl-nitrene followed by formation of the α-oriented aziridine intermediate (**14**) presumably due to the presence of β-acetoxy group at C-3.[19] The aziridine would be opened with the alcohol at C-1 from the β-face to afford 1,2- and 2,3-di-*trans*-product.



Scheme 1 Proposed reaction pathway

The trichloroethoxysulfonyl group in **3a** was removed by treatment with zinc and acetic acid in the presence of $CuSO_4$ to give the free amine **15**. When the desulfonylation was carried out in the presence of acetic anhydride, the acetamide **16** was obtained in good yield.



Scheme 2 Deprotection of the trichloroethoxysulfonyl group

In conclusion, we have developed a regio- and stereo-selective synthesis of 2-amino-2-deoxy-1-*O*-β-glycosides from acetylated glycals via rhodium(II)-catalysed intermolecular aziridination with trichloroethoxysulfonamide and iodosobenzene. This amidoglycosylation proceeds smoothly under mild conditions without the use of usual *O*-glycosylation promoters such as Lewis acids, and is applicable to a variety of primary and secondary alcohols.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, analytical data, copies of ^{1}H and ^{13}C NMR, and mass spectra. See DOI: 10.1039/b000000x/

‡ 2-(Trichloroethoxysulfonylamino)methyltetrahydrofuran was obtained in *ca*. 0.5 molar ratio to major product **8b**.

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