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Synthesis of D-Glycopyranosyl Azides from 1,2-Anhydrosugars Using Lithium Azidohydridodiisobutylaluminate

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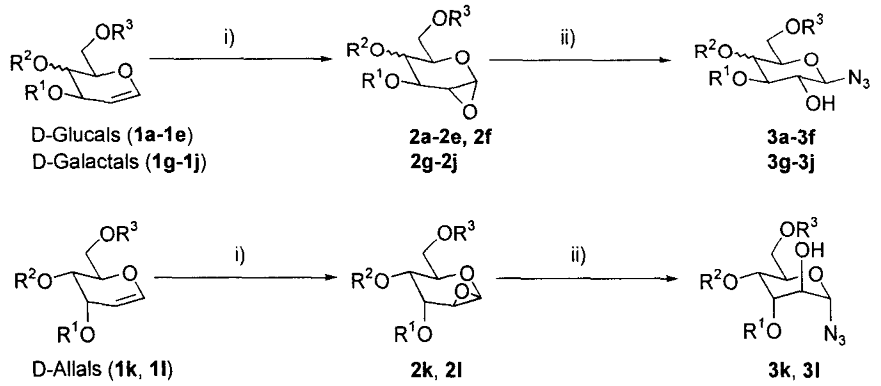
Abstract

1,2-Anhydrosugars were transformed regio- and stereoselectively into the corresponding D-glycopyranosyl azides in high yield by treatment with lithium azidohydridodiisobutylaluminate in THF.

Keywords: Aluminum and compounds; Azides; Glycosides; Stereoselection

We have recently reported lithium azidohydridodiisobutylaluminate (DIBAH-LiN$_3$) [1] and lithium *B*-azido-*B*-hydrido-9-BBN [2] transfer an azido group to the epoxides regioselectively to produce *vic*-azidoalcohols. In connection with these results, we have also applied lithium azidohydridodiisobutylaluminate to 1,2-anhydrosugars to synthesize D-glycopyranosyl azides, the precursors for the glycoconjugate synthesis.



i) DMDO (2eq), CH$_2$Cl$_2$-CH$_3$COCH$_3$, 0 ℃, 1 h ii) DIBAH-LiN$_3$ (2eq), THF, 0 ℃, 1 h

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1,2-Anhydrosugars were prepared stereospecifically and quantitatively through direct epoxidation of the corresponding D-glycals with 3,3-dimethyldioxirane (DMDO) [3,4,5]. D-Glucals (**1a-1e**) and D-galactals (**1g-1j**) afforded the corresponding 1α,2α-anhydrosugars (**2a-2e, 2g-2j**) whereas D-allals (**1k,1l**) gave 1β,2β-anhydrosugars (**2k, 2l**) stereoselectively [6]. This stereochemical outcome is probably due to the configuration of the 3-OH protected with relatively bulky groups. 1α,2α-Anhydro-3,4,6-tri-*O*-acetyl-D-glucopyranose (**2f**) was also prepared from D-glucose in 4 steps [7].

Treatment of these 1,2-anhydrosugars with lithium azidohydridodiisobutylaluminate (DIBAH-LiN_3) (2eq) in THF afforded D-glycopyranosyl azides in 64–92% yield even though the reaction condition was not optimized. Nucleophilic attack of the azido group to the more positive anomeric carbon gave rise to the regio- and stereoselectivity of this epoxide-opening reaction. A typical reaction procedure is as follows: DIBAH (0.2 ml of 1*M* solution in THF, 0.2 mmol) was added to a stirred suspension of lithium azide (9.8 mg, 0.2 mmol) in THF (1 ml) under argon atmosphere at rt. The mixture was stirred for 30 min and the resulting clear solution was cooled to 0 ℃. A solution of 1α,2α-anhydro-3,4,6-tri-*O*-benzyl-D-glucopyranose (**2a**, 44 mg, 0.1 mmol) in THF (1 ml) was added and the solution was stirred at 0 ℃ for 1 h. The mixture was poured into the saturated aqueous sodium bicarbonate solution (3 ml) and extracted with chloroform (3 x 5 ml). The organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated. Silica gel column chromatography afforded 3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl azide (**3a**) in 73% yield. The results are summarized in the Table.

Table. Reaction of 1,2-Anhydrosugars with DIBAH-LiN_3

Anhydro-sugars	Protective Groups	Products	Isolated Yield(%)	Anhydro-sugars	Protective Groups	Products	Isolated Yield(%)
2a	$R^1 = R^2 = R^3 = Bn$	**3a**	73	**2g**	$R^1 = R^2 = R^3 = Bn$	**3g**	78
2b	$R^1 = R^2 = R^3 = TBS$	**3b**	64	**2h**	$R^1,R^2 = {>}CO$, $R^3 = TBDPS$	**3h**	65
2c	$R^1 = Bn$, $R^2,R^3 = {>}C(CH_3)_2$	**3c**	75	**2i**	$R^1 = Bn$, $R^2,R^3 = {>}CHPh$	**3i**	70
2d	$R^1 = Bn$, $R^2,R^3 = {>}CHPh$	**3d**	80	**2j**	$R^1 = TBS$, $R^2,R^3 = {>}CHPh$	**3j**	72
2e	$R^1 = TBS$, $R^2,R^3 = {>}CHPh$	**3e**	92	**2k**	$R^1 = Bn$, $R^2,R^3 = {>}CHPh$	**3k**	76
2f	$R^1 = R^2 = R^3 = Ac$	**3f**	71	**2l**	$R^1 = TBS$, $R^2,R^3 = {>}CHPh$	**3l**	80

In conclusion, a mild and facile method for the preparation of D-glycopyranosyl azides from 1,2-anhydrosugars has been established by using lithium azidohydridodiisobutylaluminate in THF [8].

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References and notes

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[6] A typical epoxidation procedure is as follows: 3,4,6-Tri-*O*-benzyl-D-glucal (**1a**, 0.1 mmol) was dissolved in CH_2Cl_2 (10 ml) and the resulting solution was cooled to 0 ℃. A solution of dimethyldioxirane in acetone (0.2 mmol, 0.05-0.1*M*) was added dropwise and the reaction mixture was stirred at 0 ℃ for 1 h. Solvent removal with a stream of dry nitrogen and vacuum drying afforded 1α,2α-anhydro-3,4,6-tri-*O*-benzyl-D-glucopyranose (**2a**) in quantitative yield.

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[8] 1,2-Anhydrosugars and D-glycopyranosyl azides were identified through ^{1}H-NMR, IR, and $[\alpha]_D$ values.