Glycal Cyclization

$InBr_3$-Catalyzed Cyclization of Glycals with Aryl Amines**

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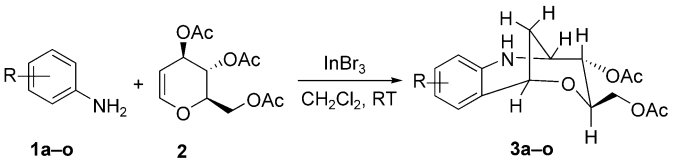
Dedicated to Professor Goverdhan Mehta on the occasion of his 60th birthday

Glycals are ambident electrophiles capable of reacting with various nucleophiles such as alcohols, malonates, and silyl nucleophiles under the influence of acid catalysts or oxidants to produce 2,3-unsaturated glycosides.[1,2] In recent times, indium halides have emerged as versatile Lewis acid catalysts imparting high regio-, chemo-, and diastereoselectivity to a variety of organic transformations.[3] Compared to conventional Lewis acids, indium tribromide, in particular, has advantages of low catalyst loading, moisture stability, and catalyst recycling.[4] C-Glycosides bearing carbon-linked heterocycles have attracted great attention owing to their potent antiviral and antitumor behavior.[5] Because of these properties of aryl glycosides, we have attempted C-glycosidation with aryl amines to synthesize aryl C-glycosides with a free amino functionality for further derivatization. Interestingly, we observed for the first time an unusual formation of benzo-fused heterobicycles in the aminoglycosidation.

In our continuing research on glycoside synthesis,[6] we have made unprecedented observations in the aminoglycosidation reactions of glycals with aryl amines, which we report here. Initially, we attempted the aminoglycosidation reaction of D-glucal with aniline using 10 mol% indium(III) bromide as a novel glycosyl activator. Interestingly, the unusual bicyclic adduct **3a** (R = H) was isolated in 85% yield with high stereoselectivity (Scheme 1).



Scheme 1. Reaction of 3,4,6-tri-*O*-acetyl-D-glucal (**2**) with aryl amines.

The product **3a** was characterized thoroughly by various NMR experiments including double-quantum-filtered correlation spectroscopy (DQFCOSY), nuclear Overhauser effect spectroscopy (NOESY), heteronuclear single-quantum correlation spectroscopy (HSQC),[7] and $^3J_{CH}$-optimized HMBC experiments.[8] The edited HSQC spectrum showed the presence of two methylene groups in addition to eight methine and two methyl groups. The location of the methylene group in the bridge of a bicyclononene-like structure was confirmed by the presence of small couplings between these protons and the bridgehead protons H1 and H3 ($J_{H1\text{-}H2(pro\text{-}S)} = 3.7$ Hz, $J_{H1\text{-}H2(pro\text{-}R)} = 1.8$ Hz, $J_{H2(pro\text{-}S)\text{-}H3} = 2.4$ Hz, and $J_{H2(pro\text{-}R)\text{-}H3} = 4.6$ Hz; Figure 1)). Fusion of the bicyclononene and the aromatic ring at C1–C11 and NH–C3 was confirmed by nOe interactions between H1 and H12. Further support for the structure came from HMBC peaks for H1/C12, H1/C11, H1/C16 and H12/C1. The two six-membered rings of the bicyclononane moiety have two different conformations. The one containing oxygen takes a chair form,

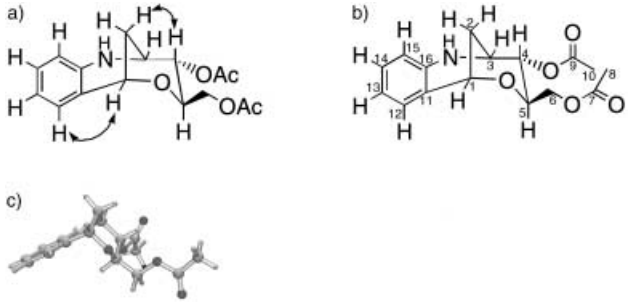


Figure 1. a) Characteristic nOe interactions, b) the chemical structure, and c) the energy-minimized structure of **3a**.

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whereas the other ring with nitrogen and fused to the aromatic ring exists in half-chair form. HMBC peaks for $H2_{(pro\text{-}S)}$/C11 and $H2_{(pro\text{-}R)}$/C4 are consistent with this structure. The large coupling constant $J_{H4\text{-}H5} = 10.4$ Hz and the NOESY cross peak for $H2_{(pro\text{-}S)}$/H4 further support the chair form for the ring containing these protons. The ring current of the aromatic ring causes high-field chemical shifts for $H2_{(pro\text{-}R)}$ ($\delta = 1.96$ ppm) and H5 ($\delta = 3.58$ ppm). Further the structure of **3a** was confirmed by molecular mechanics calculations.[9]

These unexpected results encouraged us to extend this process to other glycals and aryl amines. Interestingly, α-naphthylamine and substituted aryl amines such as electron-rich as well as electron-deficient aniline derivatives reacted efficiently with D-glucal under similar conditions to produce the corresponding cyclic adducts in fairly good yields (Table 1). Similarly, L-rhamnal also underwent cyclization with aryl amines to produce derivatives **3p** and **3q**. Under similar reaction conditions D-xylal also underwent cyclization with aryl amines to afford the corresponding cyclic adducts **3r** and **3s**.

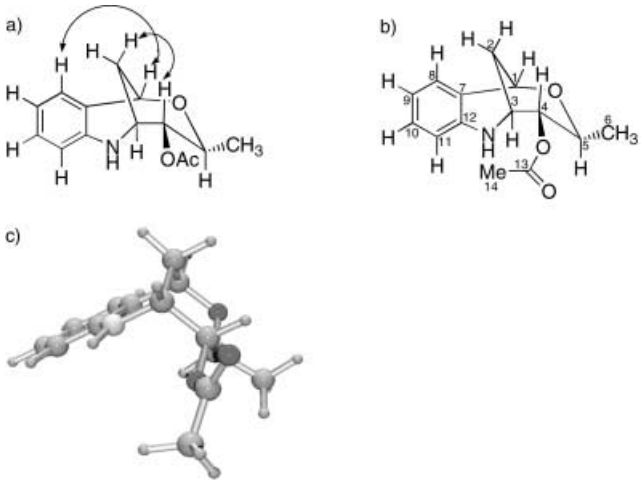


Figure 2. Characteristic nOe interactions, the chemical structure, and the energy-minimized structure of **3p**.

Table 1: Synthesis of oxaazatricyclotridecatrienyl derivatives from D-glucal and aryl amines (see Scheme 1).

Glucal	Amine	Product[a]	$InBr_3$ (10 mol%)		TMSOTf (1 equiv)	
			t [h]	Yield [%][b]	*t* [h]	Yield [%][b]
D-glucal	$C_6H_5NH_2$ (**1a**)	**3a**	6.0	85	3.5	87
D-glucal	2-$MeC_6H_4NH_2$ (**1b**)	**3b**	5.5	82	4.0	85
D-glucal	4-$FC_6H_4NH_2$ (**1c**)	**3c**	7.0	78	5.0	81
D-glucal	4-$ClC_6H_4NH_2$ (**1d**)	**3d**	6.0	84	4.5	85
D-glucal	2-Br-4-Me-$C_6H_3NH_2$ (**1e**)	**3e**	8.0	75	6.0	82
D-glucal	α-naphthylamine (**1f**)	**3f**	9.0	80	5.0	75
D-glucal	4-Br-$C_6H_4NH_2$ (**1g**)	**3g**	7.5	82	4.5	84
D-glucal	4-MeO-$C_6H_4NH_2$ (**1h**)	**3h**	7.0	78	4.0	78
D-glucal	2-Cl-$C_6H_4NH_2$ (**1i**)	**3i**	6.0	80	5.0	83
D-glucal	4-$MeC_6H_4NH_2$ (**1j**)	**3j**	5.5	85	4.5	89
D-glucal	3-Cl-$C_6H_4NH_2$ (**1k**)	**3k**	6.0	80[c]	5.0	82[c]
D-glucal	2,5-$(CH_3)_2$-$C_6H_3NH_2$ (**1l**)	**3l**	5.0	83	4.5	85
D-glucal	2,6-$(CH_3)_2$-$C_6H_3NH_2$ (**1m**)	**3m**	8.0	n.r.[d]	6.0	n.r.[d]
D-glucal	3-Cl-4-F-$C_6H_3NH_2$ (**1n**)	**3n**	7.0	77	6.0	78
D-glucal	2,4-Cl_2-$C_6H_3NH_2$ (**1o**)	**3o**	6.0	79	5.0	81
L-rhamnal	$C_6H_5NH_2$ (**1a**)	**3p**	5.0	87	5.0	85
L-rhamnal	4-$MeC_6H_4NH_2$ (**1j**)	**3q**	4.5	82	4.0	84
D-xylal	$C_6H_5NH_2$ (**1a**)	**3r**	6.0	89	3.5	82
D-xylal	4-$MeC_6H_4NH_2$ (**1j**)	**3s**	5.0	85	4.0	80

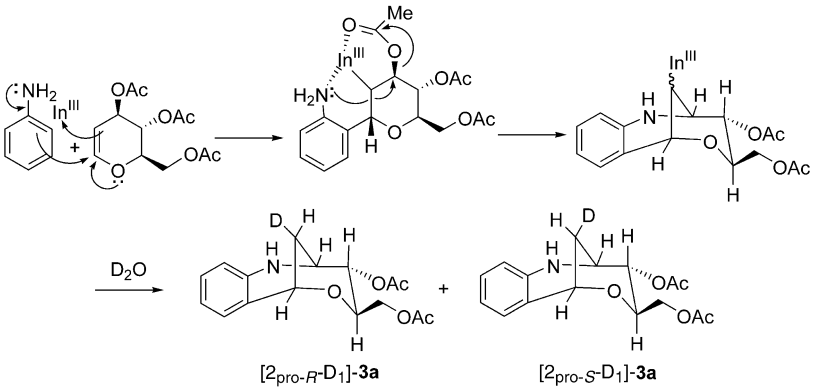
[a] Products were characterized by ^1H NMR, ^{13}C NMR, IR spectroscopy and mass spectrometry. [b] Yield refers to pure products after chromatography. [c] Ratio of regioisomers 7:3. [d] No reaction.

The conformation of product **3p** was similar to that of **3a** (Figure 2). The appearance of small coupling constants, $J_{H1\text{-}H2(pro\text{-}R)} = 3.6$ Hz, $J_{H1\text{-}H2(pro\text{-}S)} = 1.9$ Hz, $J_{H2(pro\text{-}R)\text{-}H3} = 2.6$ Hz, and $J_{H2(pro\text{-}S)\text{-}H3} = 4.4$ Hz, indicates that the observed conformation is like bicyclononene, with the middle six-membered ring in a half-chair conformation. The nOe cross peak for H1/H8, and $H2_{(pro\text{-}R)}$/H4 as well as coupling constant $J_{H4\text{-}H5} = 10.1$ Hz confirms that the six-membered ring is in a chair conformation.

To elucidate the mechanistic pathway, we carried out the reaction with deuterated aniline and 3,4,6-tri-*O*-acetyl-D-glucal (**2**), but no deuterium incorporation was observed in the product. However, the reaction of aniline and **2** in D_2O at 80 °C gave the isomeric deuterated products [$2_{pro\text{-}R}$-D_1]-**3a** and [$2_{pro\text{-}S}$-D_1]-**3a** in equal amounts, which was confirmed by ^1H NMR and FAB mass spectroscopy.[10] This clearly indicates that protons were abstracted from the solvent and not from aniline.

We also found that **2** does not react with 2,6-dimethylaniline (Table 1), which clearly indicates that one of the *ortho* positions of aniline should be free from substitution for the success of the reaction. Accordingly, a plausible mechanism for the formation of product **3** may be depicted[11] as in Scheme 2.

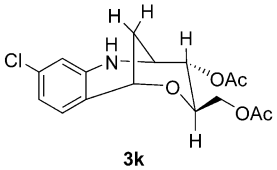
Although further study is needed to settle the reaction mechanism, this method is a highly stereoselective, one-pot synthesis of unusual tricyclic heterocycles under mild conditions. The efficacy of various Lewis acids such as $InBr_3$, $InCl_3$, $CeCl_3 \cdot 7H_2O$, YCl_3, and $YbCl_3$ was tested for this conversion. Indium tribromide was found to be the most effective catalyst in terms of conversion and selectivity. For instance, treatment of **2** with aniline in the presence of 10 mol% $InBr_3$ and 10 mol% $InCl_3$ for 6 h afforded the **3a** yields of 85% and 72%, respectively. However, in the absence of $InBr_3$ or $InCl_3$, the reaction did not proceed even after an extended time. Various triflates were screened—TMSOTf, $Sc(OTf)_3$, $Bi(OTf)_3$, $Yb(OTf)_3$, $Ce(OTf)_3$ and $Sm(OTf)_3$—and a stoichiometric amount of TMSOTf was found to be best for this reaction.



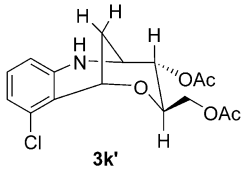
Scheme 2. A possible reaction mechanism.

The scope and generality of this process is illustrated with various glycals and aryl amines (Table 1). It is important to mention that the simple cyclic enol ethers such as 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran afforded the corresponding tetrahydroquinoline derivatives under similar reaction conditions.[12] The coupling reaction of aryl amines with D-glucal also proceeded smoothly in the presence of 10 mol% $InBr_3$ in water at 80 °C with similar yields and selectivity although with longer reaction times (8–12 h). Furthermore, the reaction also proceeded with protic acid, specifically montmorillonite KSF, at 80 °C in 1,2-dichloroethane to yield the desired product.

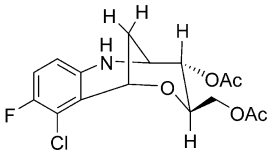
The scope of this method was investigated with respect to various glycals and a wide range of anilines including *ortho*-, *meta*-, *para*-, mono-, and disubstituted anilines, and the results are presented in the Table 1. However, in case of *meta*-chloroaniline, the product obtained was a mixture of two regioisomers **3k** and **3k′** in 7:3 ratio; the reaction with 3-chloro-4-fluoroaniline gave only a single product 3n.



3k



3k'



3n

In summary, we disclose a novel one-pot synthesis of new carbohydrate derivatives, benzo-fused heterobicycles, from glycals and aryl amines using a catalytic amount of indium tribromide under extremely mild and convenient conditions. Alternatively, a stoichiometric amount of TMSOTf can also be used to produce these products with an unusual tetrahydroquinoline motif. This is an entirely new approach to functionalize glycals with aryl amines, leading to a biologically well-defined tetrahydroquinoline framework.

Experimental Section

A mixture of D-glucal (1 mmol), aryl amine (1 mmol), and indium tribromide (10 mol%) or TMSOTf (1 mmol) in dichloromethane (10 mL) was stirred at 27 °C for the appropriate time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water and extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate/hexane 1:9) to afford pure cyclic adduct.

Characterization of selected products: **3a**: liquid, $[\alpha]_D = 95.5$ ($c = 1.0$, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.16$ (dt, $J = 1.5$, 7.9 Hz, 1H, H13), 7.13 (dd, $J = 1.5$, 7.9 Hz, 1H, H15), 6.69 (dt, $J = 1.5$, 7.9 Hz, 1H, H14), 6.61 (dd, $J = 1.5$, 7.9 Hz, 1H, H12), 4.84 (dd, $J = 3.1$, 10.4 Hz, 1H, H4), 4.81 (dd, $J = 1.8$, 3.7 Hz, 1H, H1), 4.44 (brs, 1H, NH), 4.19 (dd, $J = 4.2$, 12.0 Hz, 1H, H6), 3.99 (dd, $J = 2.2$, 12.0 Hz, 1H, H6′), 3.84 (ddd, $J = 2.4$, 3.1, 4.6 Hz, 1H, H3), 3.58 (ddd, $J = 2.1$, 4.2, 10.4 Hz, 1H, H5), 2.29 (ddd, $J = 2.4$, 3.7, 13.2 Hz, 1H, $H2_{(pro\text{-}S)}$), 2.10 (s, 3H, 10-Me), 2.06 (s, 3H, 8-Me), 1.96 ppm (ddd, $J = 1.8$, 4.6, 13.2 Hz, 1H, $H2_{(pro\text{-}R)}$); ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): $\delta = 170.8$ (C7), 169.8 (C9), 145.0 (C11), 130.5 (C15), 129.9 (C13), 118.8 (C16), 117.2 (C14), 112.9 (C12), 71.8 (C4), 68.5 (C1), 67.4 (C5), 63.0 (C6), 46.6 (C3), 27.9 (C2), 21.0 (C10), 20.7 ppm (C8); FAB MS: *m*/*z*: 305 [M^+], 259, 191, 144, 130, 119, 91, 69, 57.

3p: solid; m.p. 147 °C; $[\alpha]_D = -172.3$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.14$ (dt, $J = 1.3$, 7.4 Hz, 1H, H9), 7.13 (dd, $J = 1.3$, 7.4 Hz, 1H, H11), 6.68 (dt, $J = 1.3$, 7.4 Hz, 1H, H10), 6.60 (dd, $J = 1.3$, 7.4 Hz, 1H, H8), 4.71 (dd, $J = 1.9$, 3.6 Hz, 1H, H1), 4.60 (dd, $J = 3.2$, 10.1 Hz, 1H, H4), 4.41 (brs, 1H, NH), 3.76 (ddd, $J = 2.6$, 3.2, 4.4 Hz, 1H, H3), 3.47 (dq, $J = 6.1$, 10.1 Hz, 1H, H5), 2.25 (ddd, $J = 2.6$, 3.6, 13.2 Hz, 1H, $H2_{(pro\text{-}R)}$), 2.21 (s, 3H, $COCH_3$), 1.95 (ddd, $J = 1.9$, 4.4, 13.2 Hz, 1H, $H2_{(pro\text{-}S)}$), 1.08 ppm (d, $J = 6.1$ Hz, 3H, 6-Me). ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): $\delta = 170.1$ (C13), 145.2 (C7), 130.4 (C11), 129.6 (C9), 119.7 (C12), 117.0 (C10), 112.8 (C8), 78.1 (C4), 68.3 (C1), 64.9 (C5), 46.8 (C3), 28.3 (C2), 21.1 (C14), 18.0 ppm (C6). FAB MS: *m*/*z*: 247 [M^+], 188, 176.

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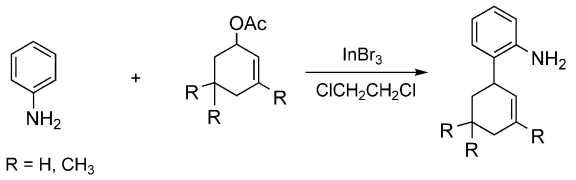
[1] a) R. J. Ferrierm, N. J. Prasad, *Chem. Commun.* **1969**, 570; b) R. J. Ferrier, *Adv. Carbohydr. Chem. Biochem.* **1969**, *24*, 199.
[2] M. H. D. Postema, *Tetrahedron* **1992**, *48*, 8545.
[3] a) C. J. Li, T. H. Chan, *Tetrahedron* **1999**, *55*, 11149; b) G. Babu, P. T. Perumal, *Aldrichimica Acta* **2000**, *33*, 16; c) R. Ghosh, *Indian J. Chem. Sect. B* **2001**, *40*, 550.
[4] a) M. A. Ceschi, L. A. Felix, C. Peppe, *Tetrahedron Lett.* **2000**, *41*, 9695; b) M. Bandini, P. Giorgio, P. G. Cozzi, M. Giocomini, P. Melchiorre, S. Selva, A. Umani-Ronchi, *J. Org. Chem.* **2002**, *67*, 3700.
[5] a) M. P. Mingeot-Leclercq, Y. Glupczynski, P. M. Tulkens, *Antimicrob. Agents Chemother.* **1999**, *43*, 727; b) M. J. Dianez, J. Galan, A. Gomez-Sanchez, A. Lopez-Castra, M. Rico, *J. Chem. Soc. Perkin Trans. 1* **1987**, 581.
[6] a) J. S. Yadav, B. V. S. Reddy, *Synthesis* **2002**, 511; b) J. S. Yadav, B. V. S. Reddy, A. K. Raju, C. V. Rao, *Tetrahedron Lett.* **2002**, *43*, 5437.

[7] J. Cavanagh. W. J. Fairbrother, A. G. Palmer III, N. J. Skelton, *Protein NMR Spectroscopy*, Academic Press, San Diego, **1996**.
[8] C. E. Hadden, G. E. Martin, V. V. Krishnamurthy, *Magn. Reson. Chem.* **2000**, *38*, 143 – 147.
[9] a) H. Goto, E. J. Osawa, *J. Chem. Soc. Perkin Trans. 2* **1993**, 187; b) P. C. MODEL, Serena Software Box 3076, Bloomington, IN, USA.
[10] For the ionization potential of indium see: a) P. Cintas, *Synlett* **1995**, 1087; b) N. Fujiwara, Y. Yamamoto, *J. Org. Chem.* **1997**, *62*, 2318.
[11] The reaction of cyclohexenyl acetate and aniline under the influence of 10 mol% $InBr_3$ in dichloroethane at 80 °C afforded 2-(2-cyclohexenyl)aniline, which supports the formation of the initial C–C bond at the *ortho* position of the aryl amine.



[12] J. S. Yadav, B. V. S. Reddy, K. Sadasiv, P. S. R. Reddy, *Tetrahedron Lett.* **2002**, *43*, 3853.

