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$Sc(OTf)_3$-catalyzed *C*-glycosidation of glycals: a facile synthesis of allyl glycosides, glycosyl cyanides and glycosyl azides†

J. S. Yadav,* B. V. Subba Reddy and Pratap K. Chand

Organic Chemistry Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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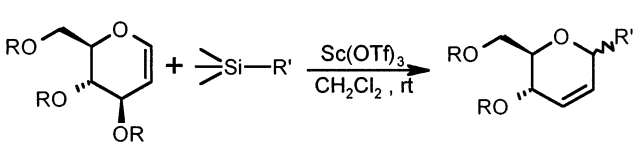
Abstract—The treatment of glycals with allyltrimethylsilane, trimethylsilyl cyanide and trimethylsilyl azide in the presence of catalytic amounts of $Sc(OTf)_3$ gave the corresponding 2,3-unsaturated allyl glycosides, glycosyl cyanides and glycosyl azides in excellent yields with high α-selectivity.

The *C*-glycosidation reaction is an important transformation for the introduction of a carbon chain into sugars. *C*-Glycosides are versatile chiral building blocks for the synthesis of biologically active natural products.[1] Particularly, allyl glycosides are attractive due to the presence of a terminal double bond that is amenable to easy functionalization leading to other chiral molecules as well as to other carbohydrate analogues.[2] In addition, glycosyl azides are important precursors for the synthesis of glycosyl amines, glycopeptides and glycoproteins. Further, glycosyl cyanides are useful chiral intermediates[3] for the synthesis of *C*-glycosyl derivatives because the cyano group can be readily transformed into a variety of other functional groups. Also, they have been used as precursors for the synthesis of naturally occurring *C*-nucleoside antibiotics and many analogues.[4] As a result, there have been reports on the synthesis of *C*-glycosides[5,6] that utilize $TiCl_4$, $BF_3{\cdot}OEt_2$, TMSOTf and SnF_4 as promoters. Recently, DDQ and $InCl_3$ have also been used as effective promoters[7] for the synthesis of allyl glycosides. However, most of these procedures involve stoichiometric amounts of catalysts, harsh reaction conditions and long reaction times and give unsatisfactory yields and low stereoselectivity. Furthermore, these promoters cannot be recovered and reused because they decompose under the quenching conditions. Unlike the traditional Lewis acids, $TiCl_4$, $BF_3{\cdot}OEt_2$, TMSOTf and $SnCl_4$, lanthanide triflates are highly oxophilic and form strong but labile bonds with oxygen donor ligands. This feature has often allowed sub-stoichiometric amounts of the Lewis acid to be used to promote a variety of reactions. Indeed, such Lewis acids are effective catalysts for many fundamental reactions,[8] including Diels–Alder reactions, Michael reactions, Friedel–Crafts acylations, Mukaiyama aldol reactions and Sakurai allylation reactions. Since $Sc(OTf)_3$ has unique catalytic properties for carbon–carbon bond forming reactions, the use of $Sc(OTf)_3$ as a catalyst for the *C*-glycosidation of glycals with silyl nucleophiles is of interest.

In continuation of our work on the applications of scandium triflate for various transformations,[9] we report here a mild and highly efficient protocol for *C*-glycosidation of glycals with allyltrimethylsilane and trimethylsilyl cyanide using $Sc(OTf)_3$ as the catalyst. The reaction of 3,4,6-tri-*O*-acetyl-D-glucal with allyltrimethylsilane in the presence of 3 mol% scandium triflate led to the formation of the 2,3-unsatuarated allyl glycoside in 93% yield with high α-selectivity (Scheme 1).

The predominant formation of the α-anomer may arise from a thermodynamic anomeric effect. Similarly, the



R = Ac , Bz , Piv R' = Allyl , Cyanide , Azide

Scheme 1.

Keywords: scandium triflate; glycals; *C*-glycosidation; 2,3-unsaturated glycosides.

* Corresponding author. Tel./fax: +91-40-7170512; e-mail: yadav@iict.ap.nic.in

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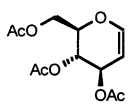
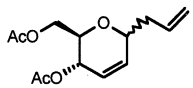
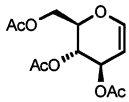
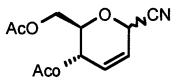
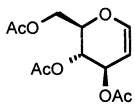
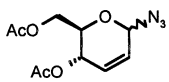
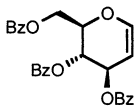
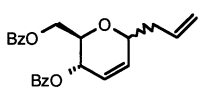
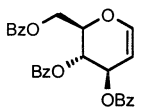
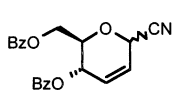
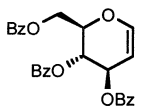
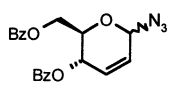
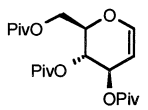
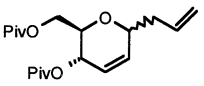
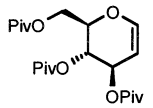
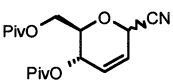
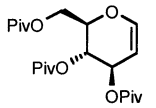
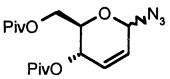
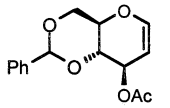
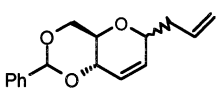
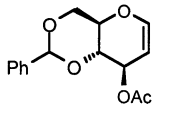
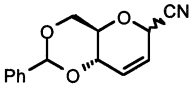
treatment of various glycals with allyltrimethylsilane gave the corresponding allyl glycosides in excellent yields. Furthermore, the reaction of glycals with trimethylsilyl cyanide afforded the corresponding glycosyl cyanide in high yields in short reaction times. The reaction of trimethylsilyl azide with glycals in the presence of $Sc(OTf)_3$ gave the corresponding glycosyl azides in good yields. As shown in Table 1, these glycosidation reactions proceeded smoothly at room temperature in the presence of 3 mol% of scandium triflate in dichloromethane. The reactions were completed within 3.5–8.0 h to give high yields of *C*-glycosides with the α-anomers as the major products. However, the reactions of 3,4,6-tri-*O*-benzoyl- and 3,4,6-tri-*O*-pivolyl-D-glucal required longer reaction times as well as higher loading of the catalyst (5% w/w of glucal) to achieve yields comparable with those of the acetylated analogues. Furthermore, the reactions of benzylidene protected glycals with allyltrimethylsilane and trimethylsilyl cyanide in presence of 3% scandium triflate proceeded smoothly at room temperature without hydrolysis of benzylidene group, whereas the same transformation in the presence of $BF_3{\cdot}OEt_2$ or $TiCl_4$ proceeded with the hydrolysis of benzylidene group.

Table 1. $Sc(OTf)_3$-catalyzed glycosidation of silyl nucleophiles

Entry	Substrate (1)	Product (2)	Reaction time (h)	Yields [a] (%)	Anomeric Ratio [b]
a			3.5	93	9 : 1
b			4.0	90	6 : 4
c			4.5	88	7 : 3
d			5.0	90	9 : 1
e			6.0	87	6 : 4
f			8.0	85	7 : 3
g			4.0	95	9 : 1
h			4.5	84	6 : 4
i			5.5	86	7 : 3
j			3.5	90	9 : 1
k			4.0	87	6 : 4

[a] *Isolated yields as pure anomeric mixtures after purification*

[b] *Anomeric ratio was determined on the basis of the integrated ratios of the anomeric hydrogens in the ^1H NMR spectra*

There are several advantages to the use of scandium triflate as catalyst for this transformation which include high yields of the products, very small quantities of the catalyst, reusability of the catalyst, short reaction times and high α-selectivity. All the products were characterized by ^{1}H, ^{13}C NMR and IR spectra and also by comparison with authentic compounds. The ratio of α- and β-anomers was established by ^{1}H NMR spectra. The spectroscopic data of the products were identical with the data reported in the literature.[10] The results, as summarized in Table 1, reveal the scope and generality of this reaction with respect to various glycals and nucleophiles. The catalyst scandium triflate was easily recovered from the aqueous layer on work up and reused without significant loss of activity.[11]

In summary, scandium triflate was found to be an efficient and reusable catalyst for the *C*-glycosidation of glycals with various nucleophiles. This procedure offers several advantages over existing procedures, including mild reaction conditions, high yields of products, short reaction times, greater anomeric selectivity, very small quantity of the catalyst, regeneration of the catalyst, and simple experimental/isolation procedures, which make it an attractive alternative to existing methodology.

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11. **General procedure**: A mixture of 3,4,6-tri-*O*-acetyl-D-glucal (5 mmol), the silyl nucleophile (5 mmol) and scandium triflate (3% w/w of glucal) in dichloromethane (10 mL) was stirred at room temperature. After complete conversion, as indicated by TLC, the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (2×15 mL). The organic layers were dried over anhydrous Na_2SO_4 and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 2:8) to afford pure glycoside. The aqueous layer was concentrated in vacuo to recover the catalyst. Spectroscopic data for **2a**: ^{1}H NMR ($CDCl_3$) δ: 2.08 (s, 6H), 2.35–2.45 (m, 2H), 3.95 (dt, 1H, $J=6.5$ and 3.7 Hz), 4.10–4.20 (m, 2H), 4.25–4.30 (m, 1H), 5.05–5.20 (m, 3H), 5.75–5.95 (m, 3H). ^{13}C NMR (proton decoupled, $CDCl_3$) δ: *α-isomer*: 20.5, 20.8, 37.7, 62.8, 64.9, 69.8, 71.3, 117.4, 123.5, 132.5, 134.0, 169.7, 170.2; *β-isomer*: 20.5, 20.8, 39.8, 63.7, 65.4, 73.9, 74.2, 117.4, 125.0, 132.2, 133.5, 169.7, 170.4. Compound **2b**: ^{1}H NMR ($CDCl_3$) δ: 2.10 (s, 3H), 2.12 (s, 3H), 4.05 (dt, 1H, $J=9.0$ and 4.0 Hz), 4.25 (d, 2H, $J=4.0$ Hz), 5.10 (dt, 1H, $J=3.5$ and 2.0 Hz), 5.35 (dq, 1H, $J=9.0$ and 2.0 Hz), 5.90 (dt, 1H, $J=3.5$ and 10.2 Hz), 6.05 (dt, 1H, $J=10.2$ and 2.0 Hz). IR (neat): 2950, 1755, 1748, 1652, 1438, 1370, 1225, 1108, 1040, 1010, 980, 920. ^{13}C NMR (proton decoupled, $CDCl_3$) δ: *α-isomer*: 20.5, 20.6, 62.0, 62.4, 63.5, 71.8, 115.5, 123.4, 129.4, 169.8, 169.9; *β-isomer*: 20.5, 20.6, 62.3, 62.7, 63.3, 74.2, 115.3, 124.0, 128.5, 169.8, 169.9. Compound **2I**: ^{1}H NMR ($CDCl_3$) δ: 1.15 (s, 9H), 1.20 (s, 9H), 4.15 (dt, 1H, $J=9.0$ and 4.0 Hz), 4.25 (d, 2H, $J=4.0$ Hz), 5.30 (m, 1H), 5.50 (dq, 1H, $J=9.0$ and 2.0 Hz), 5.75 (dt, 1H, $J=3.5$ and 10.2 Hz), 5.95 (dt, 1H, $J=10.2$ and 2.0 Hz). Compound **2J**: ^{1}H NMR ($CDCl_3$) δ: 2.35 (m, 1H), 2.50 (m, 1H), 3.65 (dt, 1H, $J=8.0$ and 4.2 Hz), 3.80 (t, 1H $J=10$ Hz), 4.15 (dq, 1H, $J=8.0$ and 2.1 Hz), 4.25–4.35 (m, 2H), 5.05–5.15 (m, 2H), 5.60 (s, 1H), 5.75 (dt, 1H, $J=10$ and 2.1 Hz), 5.80–5.90 (m, 1H), 6.05 (d, 1H, $J=10.2$ Hz), 7.25–7.40 (m, 5H).