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Indium tribromide-catalyzed highly stereoselective synthesis of alkynylsugars

J. S. Yadav,* B. V. S. Reddy, A. Krishnam Raju and C. Venkateswara Rao

Organic Chemistry Division-1, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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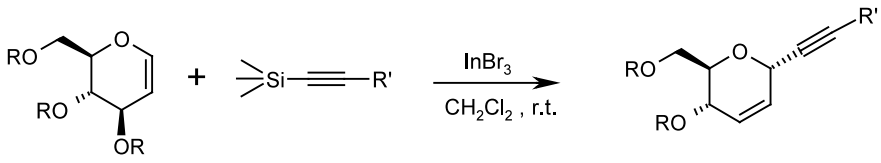
Abstract—Glycals react smoothly with alkynylsilanes in the presence of a catalytic amount of indium tribromide under mild reaction conditions to afford the corresponding alkynyl sugars in excellent yields with high α-selectivity. Alkynylation of 3,4-di-*O*-acetyl-D-xylal with alkynylsilanes afforded 1,4-*anti* adducts exclusively.

C-Glycosidation is of great significance in the synthesis of optically active compounds, since it allows the introduction of carbon chains to sugar chirons and the use of sugar nuclei as a chiral pool as well as a carbon source.[1] *C*-Glycosides are versatile chiral building blocks for the synthesis of many biologically interesting natural products such as palytoxin, spongistatin, halichondrin and many others.[2] *C*-Glycosides are potential inhibitors of carbohydrate processing enzymes and they are stable analogs of glycans involved in important intra- and intercellular processes.[3] In particular, sugar acetylenes are attractive due to the presence of a triple bond that can be easily transformed into other chiral molecules and carbohydrate analogues.[4] Furthermore, sugar acetylenes are useful precursors as chiral templates in the synthesis of many natural products such as ciguatoxin and tautomycin, etc.[5] Lewis acids such as boron trifluoride, tin tetrachloride and trimethylsilyl triflate are employed to promote *C*-alkynylation of glycals with alkynylsilanes.[6] However, many of these reagents are corrosive, moisture sensitive and are required in stoichiometric amounts. The presence of even a small amount of water causes lower yields probably due to the rapid decomposition or deactivation of the promoters. These promoters cannot be recovered because they decompose under quenching conditions. Therefore, the development of novel reagents, which are more efficient and provide convenient procedures with improved yields, is needed. In addition, there would be an advantage in developing a catalytic process for the synthesis of alkynyl sugars.

In recent years, indium halides have emerged as mild and water-tolerant Lewis acids imparting high regio- and chemoselectivity in various organic transformations.[7] Compared to conventional Lewis acids, indium halides have advantages of water stability, recyclability and simplicity in operation. Indeed, such Lewis acids are effective catalysts in promoting many fundamental reactions including Diels–Alder reactions, Michael reactions, Friedel–Crafts acylation reactions, Mukaiyama aldol reactions and Sakurai allylation reactions. In addition, indium trihalides are found to be more effective than conventional Lewis acids in promoting the cyanation of ketones, thioacetalization of carbonyl compounds and *O*-glycosidation under mild conditions.[8]



Scheme 1.

Keywords: *C*-glycosidation; indium reagents; alkynylsilanes; sugar acetylenes.

* Corresponding author. Fax: 91-40-7160512; e-mail: yadav@iict.ap.nic.in

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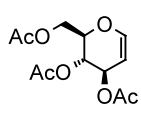
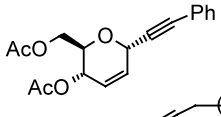
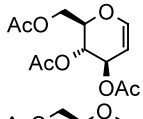
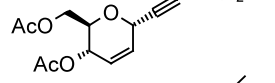
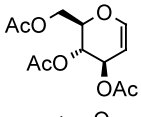
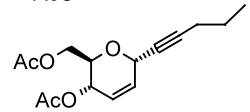
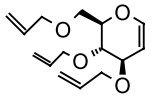
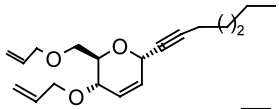
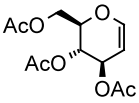
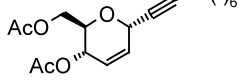
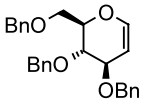
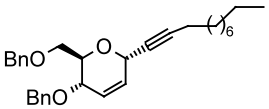
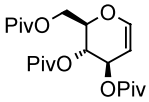
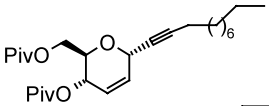
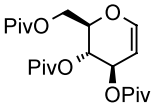
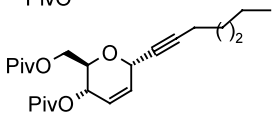
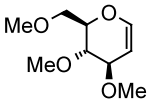
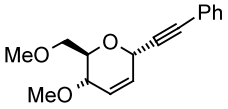
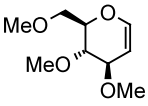
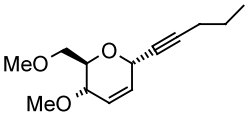
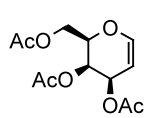
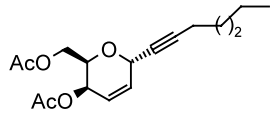
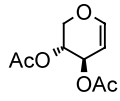
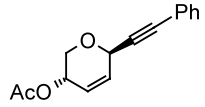
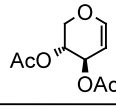
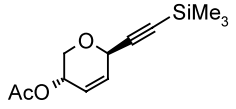
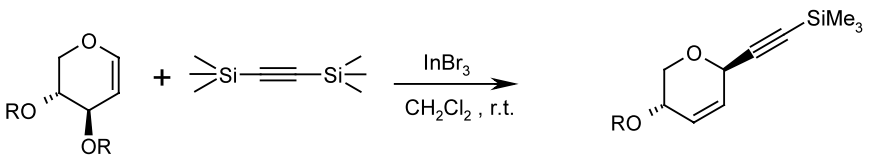
In continuation of our interest in the catalytic applications of indium halides for various organic transformations,[9] we describe herein another remarkable catalytic activity of indium tribromide in the *C*-glycosidation of glycals with alkynylsilanes (Scheme 1).

Thus, treatment of 3,4,6-tri-*O*-acetyl-D-glucal with phenyl (trimethylsilyl) acetylene in the presence of 5 mol% indium tribromide at ambient temperature results in the formation of the corresponding alkynyl *C*-glycoside in 93% yield. The α-anomer was obtained as the

Table 1. Indium(III) bromide-catalyzed syntheses of sugar acetylenes from D-glycals

Entry	Substrate (**1**)	Product[a] (**2**)	Time (h)	Yields (%)[b]
a			2.0	93
b			1.5	90
c			2.0	95
d			1.5	85
e			2.0	90
f			2.0	87
g			2.0	90
h			1.5	92
i			1.5	80
j			1.5	78
k			2.0	90
l			0.5	85[c]
m			0.5	75[c]

a:All products were characterized by ^{1}H and ^{13}C NMR spectroscopy
b:Isolated and unoptimized yields
c:Anti-selectivity was obtained in the case of pentose sugars.



Scheme 2.

predominant product in each reaction, the structures being verified by ^{1}H NMR spectroscopic data.[10] No β-anomer was observed in the ^{1}H NMR spectrum of the crude products obtained in the *C*-alkynylation of hexose sugars. In a similar fashion, various derivatives of D-glucal reacted smoothly with various alkynyltrimethylsilanes to give the corresponding alkynyl *C*-pseudoglycals in excellent yields (Table 1, entries a–j). Other glycals such as 3,4,6-tri-*O*-acetyl-D-galactal also reacted efficiently in high yield with high α-selectivity (entry k). Alkynyltrimethylsilanes reacted rapidly with D-glycals (0.5–2.0 h) to give the corresponding alkynyl *C*-glycosides in high yields with high α-selectivity. Furthermore, the treatment of 3,4-di-*O*-acetyl-D-xylal with bis(trimethylsilyl)acetylene under the influence of indium tribromide afforded trimethylsilyl ethynyl D-pseudoxylal with 1,4-*anti* selectivity (Scheme 2).

Similarly, phenyl(trimethylsilyl)acetylene reacted smoothly with D-xylal to afford the corresponding phenylethynyl *C*-glycoside in good yield (entry l). However, in the case of pentose sugars, no *syn*-adduct was observed in the ^{1}H NMR spectrum of the crude products. All products were characterized by ^{1}H, ^{13}C NMR and IR spectra and also by comparison with authentic compounds.[4,6] There are several advantages in the use of indium tribromide as catalyst for this transformation, which include high yields of products, cleaner reaction profiles, short reaction times, high α-selectivity and recoverability of the catalyst. In addition, this method avoids the use of corrosive or toxic reagents and does not require any additives or stringent reaction conditions whilst no precautions need to be taken to exclude moisture from the reaction medium. This method is simple, convenient and high yielding. The efficacies of various Lewis acids such as $InBr_3$, $InCl_3$, $In(OTf)_3$, $Sc(OTf)_3$, $Yb(OTf)_3$, YCl_3, and $YbCl_3$ were studied for this transformation. Among these catalysts, indium tribromide was found to be most effective in terms of conversion and selectivity. For example, the treatment of 3,4,6-tri-*O*-acetyl-D-glucal with phenyl (trimethylsilyl)acetylene in the presence of 5 mol% $InBr_3$ and 5 mol% $InCl_3$ for 2 h afforded 93% and 85% yields respectively. The scope and generality of this process is illustrated with respect to various glycals and alkynylsilanes. Finally, the catalyst, indium tribromide was easily recovered from the aqueous layer after work-up.[10]

In summary, this paper describes a simple and efficient method for the synthesis of alkynyl *C*-pseudoglycals from glycals and alkynylsilanes using a catalytic amount of indium tribromide under mild reaction conditions. This method provides high yields of alkynyl *C*-glycosides in a short reaction time with greater anomeric selectivity, which makes it a useful and attractive process for the synthesis of sugar acetylenes of synthetic importance.

Acknowledgements

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10. **General procedure**: A mixture of 3,4,6-tri-*O*-acetyl-D-glucal (5 mmol) and trimethylsilyl acetylene (5 mmol) and indium tribromide (5 mol%) 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, 1:9) to afford pure sugar acetylene derivative. The aqueous layer was concentrated in vacuo and the catalyst recovered quantitatively. Spectroscopic data for selected compounds:
Compound **2a** (α-anomer): liquid; $[\alpha]_D^{25} = -105.7$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.03 (s, 6H), 4.10 (ddd, 1H, $J = 3.0$, 6.5, 9.5 Hz), 4.20 (ddd, 2H, $J = 3.0$, 6.5, 12.0 Hz), 5.15 (d, 1H, $J = 1.4$ Hz), 5.25 (dd, 1H, $J = 2.2$, 8.8 Hz), 5.78 (dt, 1H, $J = 1.4$, 10.7 Hz), 5.90 (ddd, 1H, $J = 1.4$, 2.2, 10.7 Hz), 7.20–7.30 (m, 3H), 7.38–7.40 (m, 2H); ^{13}C NMR (proton decoupled, $CDCl_3$): δ 20.6, 20.9, 63.0, 64.4, 64.8, 70.0, 84.7, 86.6, 122.2, 125.4, 128.2, 128.6, 129.1, 131.7, 170.1, 170.7; IR (KBr): *v* 3024, 2125, 1745, 1577, 1402, 1219, 1092, 768, 666 cm^{-1}.
Compound **2e** (α-anomer): liquid; $[\alpha]_D^{25} = -87.5$ (*c* 3.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.9 (t, 3H, $J = 6.3$ Hz), 1.30–1.40 (m, 14H), 2.03 (s, 6H), 2.10 (t, 2H, $J = 6.5$ Hz), 4.10 (ddd, 1H, $J = 3.3$, 6.5, 9.5 Hz), 4.20 (ddd, 2H, $J = 3.3$, 6.5, 11.7 Hz), 4.90 (d, 1H, $J = 1.4$ Hz), 5.20 (dd, 1H, $J = 1.4$, 8.8 Hz), 5.70 (dt, 1H, $J = 1.4$, 10.7 Hz), 5.83 (ddd, 1H, $J = 1.4$, 2.2, 10.7 Hz); ^{13}C NMR (proton decoupled, $CDCl_3$): δ 13.9, 18.6, 20.6, 20.8, 22.5, 28.4, 28.7, 28.9, 29.1, 29.3, 31.7, 63.0, 64.1, 64.9, 69.6, 75.8, 87.6, 124.6, 130.0, 170.0, 170.6; IR (KBr): *v* 2927, 2856, 2214, 1744, 1673, 1461, 1371, 1228, 1048, 771 cm^{-1}.
Compound **2l** (α-anomer): liquid; $[\alpha]_D^{25} = +64.8$ (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.10 (s, 3H), 3.90 (d, 1H, $J = 13.1$ Hz), 4.20 (dd, 1H $J = 3.0$, 13.1 Hz), 4.90 (brs, 1H), 5.0 (brs, 1H), 5.10 (brs, 1H), 5.90 (dd, 1H, $J = 4.4$, 10.2 Hz), 6.10 (dd, 1H, $J = 3.6$, 10.2 Hz), 7.25–7.30 (m, 3H), 7.38–7.40 (m, 2H); ^{13}C NMR (proton decoupled, $CDCl_3$): δ 20.9, 63.3, 63.8, 64.1, 84.6, 96.0, 122.5, 128.1, 128.5, 131.2, 131.7, 132.0, 133.4, 133.2, 170.3; IR (KBr): *v* 3033, 2211, 1733, 1601, 1405, 1219, 1097, 778 cm^{-1}.