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Carbohydrate Research 332 (2001) 221–224

CARBOHYDRATE RESEARCH

Note

$LiBF_4$-mediated C-glycosylation of glycals with allyltrimethylsilane: a facile synthesis of allyl *C*-glycosylic compounds☆

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Received 3 January 2001; accepted 19 March 2001

Abstract

The treatment of glycals with allyltrimethylsilane in the presence of lithium tetrafluoroborate in acetonitrile gave the corresponding allyl 2,3-unsaturated *C*-glycosylic compounds in excellent yields with high anomeric selectivity.

Keywords: Lithium tetrafluoroborate; C-Glycosylation; Allyl glycosides

C-Glycosylation is an important carbon–carbon bond forming reaction in carbohydrates. *C*-Glycosylic compounds (so-called '*C*-glycosides') are versatile chiral building blocks[1] for the synthesis of biologically active natural products. In particular, allyl C-glycosylic compounds are attractive[2] due to the presence of a terminal double bond that can be easily transformed into a variety of other functional groups. As a result, there have been some reports on the synthesis of allyl *C*-glycosylic compounds via Ferrier rearrangement[3] of glycals with allyltrimethylsilane in the presence of Lewis acids.[4,5] However, many of these procedures often involve strongly acidic conditions, unsatisfactory yields, longer reaction times, and incompatibility with acid-sensitive functional groups. Therefore, the development of a neutral alternative would extend the scope of the useful C-glycosylation reaction. Recently, lithium tetrafluoroborate in acetonitrile (LTAN) has received much research attention as a mild Lewis acid in various transformations[6] including hydrolysis of acetals, desilylation of ethers, Diels–Alder reactions and O-glycosidation reactions. Unlike lithium perchlorate in diethyl ether, lithium tetrafluoroborate is non-oxidizing and non-nucleophilic; hence, it provides a convenient procedure to carry out the reactions under essentially neutral workup conditions. These unique properties of lithium tetrafluoroborate prompted us to explore this catalyst for C-glycosylation reactions.

In this report, we describe herein a novel and efficient procedure for the synthesis of allyl 2,3-unsaturated *C*-glycosylic compounds

☆ Indian Institute of Chemical Technology Communication No. 4733.

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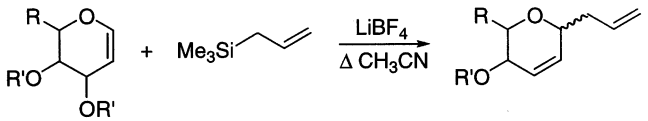
0008-6215/01/$ - see front matter
PII: S0008-6215(01)00087-8

through Ferrier rearrangement of glycals with allyltrimethylsilane using lithium tetrafluoroborate (Scheme 1).



Scheme 1. R = H, CH_3, CH_2OR'. R′ = Ac, Bz, Piv.

The reaction of 3,4,6-tri-*O*-acetyl-D-glucal with allyltrimethylsilane in the presence of lithium tetrafluoroborate in refluxing acetonitrile resulted in the formation of the allyl 2,3-unsaturated *C*-glycosylic compound in 92% yield. Likewise, several glycals were reacted with allyltrimethylsilane to afford the corresponding allyl *C*-glycosylic compounds in high yields with the α anomer as the major product. The predominant formation of the α anomer may arise from the thermodynamic anomeric effect. The reactions proceeded smoothly in refluxing acetonitrile, and the products were obtained in excellent yields with high α-selectivity. The glycals used in this reaction have been prepared by standard literature methods.[7] However, the reaction of 3,4,6-tri-*O*-benzoyl and 3,4,6-tri-*O*-pivolyl-D-glucals required longer reaction times to achieve yields comparable to those of the other acylated analogues. Further, the reaction of benzylidene-protected glucal with allyltrimethylsilane proceeded smoothly in the presence of lithium tetrafluoroborate without the hydrolysis of benzylidene group, whereas the same reaction in the presence of $BF_3{\cdot}OEt_3$ or $TiCl_4$ proceeded with the hydrolysis of benzylidene group. The products were characterized by ^1H, ^{13}C NMR and IR spectra and also by comparison with authentic compounds.[8] The spectroscopic data of the products was identical with the data reported in the literature. The product was obtained as a mixture of α and β isomers which could not be separated by column chromatography. The ratio of the α and β anomers was determined after purification by their ^1H NMR spectra. Several examples illustrating this novel and general procedure for the synthesis of *C*-glycosylic compounds are presented in Table 1

In summary, the present procedure for the synthesis of allyl 2,3-unsaturated *C*-glycosylic compounds is an attractive and useful addition to the existing ones due to experimental simplicity, high yields of products, greater selectivity, easy workup, and neutral reaction conditions. In addition to its simplicity and milder reaction conditions, this method is applicable for substrates having acid-sensitive functional groups.

1. Experimental

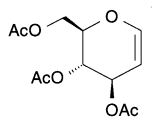
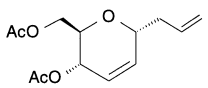
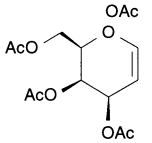
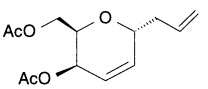
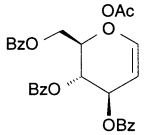
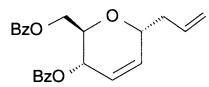
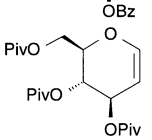
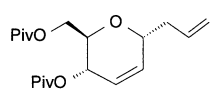
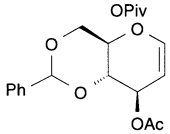
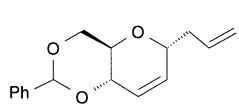
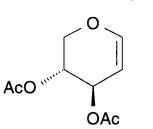
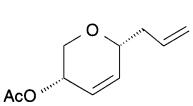
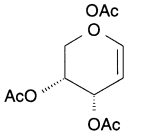
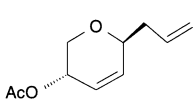
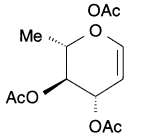
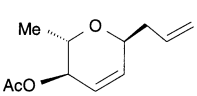
General procedure for C-glycosylation.—A mixture of glycal (5 mmol), allytrimethylsilane (7.5 mmol) and lithium tetrafluoroborate (5 mmol) was stirred in refluxing MeCN (15 mL) for an appropriate time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was quenched with water (15 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers was dried over anhyd Na_2SO_4, concentrated in vacuo, and purified by column chromatography on silica gel (E. Merck, 60–120 mesh, 1:9 EtOAc–hexane) to afford the pure allyl 2,3-unsaturated C-glycoside.

Spectral data for compounds.—**2c**: Solid, mp 74–76 °C ^1H NMR ($CDCl_3$): δ 2.35 (m, 1 H), 2.55 (m, 1 H), 4.30 (m, 1 H), 4.35 (m, 1 H), 4.50 (m, 2 H), 5.05–5.15 (m, 2 H), 5.45 (d, 1 H, *J* 8.5 Hz), 5.80 (m, 1 H), 6.05 (m, 2 H), 7.45–7.55 (m, 6 H), 8.05–8.15 (m, 4 H). ^{13}C NMR (proton decoupled, $CDCl_3$): δ 37.89, 63.78, 65.86, 69.97, 71.39, 117.60, 123.78, 128.27, 128.37, 129.70, 129.72, 129.77, 133.02, 133.12, 133.21, 134.01, 165.97, 166.33. IR (KBr): 2924, 1717, 1601, 1450, 1315, 1267, 1109 cm^{-1}. FABMS: 378 (M^+), 337, 257, 135, 105, 91, 77. Anal. Calcd for (378.43): C, 73.00; H, 5.86. Found: C, 73.08; H, 5.92.

2d: Liquid, ^1H NMR ($CDCl_3$): δ 1.20 (s, 18 H), 2.35–2.45 (m, 2 H), 4,25–4.35 (m, 3 H), 4.45 (m, 1 H), 5.05–5.20 (m, 2 H), 5.70 (m, 2 H), 5.80–5.90 (m, 1 H), 6.05 (m, 1 H). ^{13}C NMR (proton decoupled, $CDCl_3$): δ 27.06, 27.16, 38.02, 38.74, 38.81, 62.91, 64.73, 70.40, 71.28, 117.35, 123.93, 132.74, 134.10, 177.81, 178.16. IR (KBr): 2974, 2935, 2874, 1732, 1642, 1480, 1282, 1152 cm^{-1}. FABMS: 378 (M^+), 337, 257, 135, 105, 91, 77. Anal. Calcd for (338.45): C, 67.43; H, 8.93. Found: C, 67.48; H, 8.99.

2e: Liquid, ^1H NMR ($CDCl_3$): δ 2.35 (m, 1 H), 2.50 (m, 1 H), 3.65 (dt 1 H, *J* 8.0 and 4.2 Hz), 3.80 (t, 1 H, *J* 10.0 Hz), 4.15 (dq, 1 H, *J* 8.0 and 2.1 Hz), 4.25–4.35 (m, 2 H), 5.0–5.15 (m, 2 H), 5.60 (s, 1 H), 5.75 (dt, 1 H, *J* 10.2

Table 1
$LiBF_4$-mediated C-glycosylation of gylcals with allyltrimethylsiane

Entry	Substrate **1**	Product [a] **2**	Reaction time (h)	Yield [b] (%)	α/β [c]
a			3.0	92	9:1
b			4.5	90	10:0.5
c			5.0	85	9.5:1
d			5.0	87	9.5:1
e			3.0	81	9:1
f			2.5	87	9.5:1
g			3.0	85	10:1
h			2.5	90	10:1

[a] For spectroscopic data for products **2a**, **2b**, **2f** and **2g**, see Ref. 7. For product **2h**, see Ref. 6b.
[b] Isolated yields after purification.
[c] The α,β ratio was based on the integration ratios of anomeric hydrogens in the ^1H NMR spectra.

and 2.1 Hz), 5.80–5.90 (m, 1 H), 6.05 (d, 1 H, *J* 10.2 Hz), 7.30–7.45 (m, 5 H). ^{13}C NMR (proton decoupled, $CDCl_3$): δ 37.40, 68.4, 72.73, 78.74, 79.80, 99.72, 117.23, 124.21, 126.32, 128.42, 129.34, 131.27, 134.25, 136.26. IR (KBr): 2998, 2923, 1625, 1560, 1465, 1232 cm^{-1}. FABMS: 258 (M^+), 217, 167, 135, 91, 77. Anal. Calcd for (258.32): C, 74.40; H, 7.02. Found: C, 74.46; H, 7.05.

Acknowledgements

B.V.S., L.C. and K.S.R. thank CSIR, New Delhi for the award of fellowships.

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