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$CeCl_3 \cdot 7H_2O$: a novel reagent for the synthesis of 2-deoxysugars from D-glycals

J. S. Yadav,* B. V. S. Reddy, K. Bhaskar Reddy and M. Satyanarayana

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

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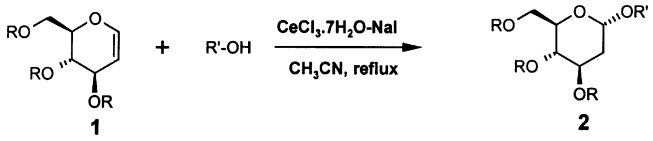
Abstract—D-Glycals react smoothly with a variety of alcohols in a highly stereoselective manner in the presence of the $CeCl_3 \cdot 7H_2O$–NaI reagent system in refluxing acetonitrile under neutral conditions to afford the corresponding 2-deoxy-α-glycopyranosides in high yields. In the absence of NaI, the glycals undergo Ferrier rearrangement under the influence of $CeCl_3 \cdot 7H_2O$ in refluxing acetonitrile to afford the corresponding 2,3-unsaturated hexopyranosides in good yields. © 2002 Elsevier Science Ltd. All rights reserved.

Deoxyglycosides are well-known structural components of several biologically active compounds, especially antitumor antibiotics such as anthracyclines, aureolic acids, orthosamycins, angucyclins, and enediynes.[1] In particular, 2-deoxy-α-glycosides are present in many bioactive natural products including compactin, olivomycin, mithramycin, daunomycin, calicheamicin and many others.[2] In this context, several methods have been developed for the preparation of 2-deoxy sugars in a multi-step sequence.[3,4] Of these, the acid-catalyzed addition of an alcohol to acetylated glycals appears to be the most direct method for the synthesis of 2-deoxy pyranosides.[5] However, only a few methods have been reported so far for the direct synthesis of 2-deoxy-α-glycosides from glycals.[5,6] To date, the generality of this process to prepare 2-deoxy sugars has remained unattractive as the protected glycals often give rearranged products under acidic conditions.[7] Thus the development of a neutral alternative such as the $CeCl_3$–NaI reagent system would extend the scope of this transformation. Lanthanide salts are unique Lewis acids[8] that are currently of great research interest. In particular, cerium reagents are relatively non-toxic, readily available at low cost and are fairly stable in water.[9]



Scheme 1.

We wish to report a mild and efficient method for the synthesis of 2-deoxyglycosides from glycals and alcohols using the $CeCl_3 \cdot 7H_2O$–NaI reagent system. Thus, treatment of 3,4,6-tri-*O*-acetyl-D-glucal with allyl alcohol in the presence of cerium(III) chloride heptahydrate–sodium iodide in acetonitrile afforded the corresponding 2-deoxyglycopyranoside in 87% yield with high α-selectivity (Scheme 1).

The α-anomer was obtained exclusively, the structure of which was characterized by spectroscopic data. The predominant formation of the α-anomer may arise from a thermodynamic anomeric effect. The reaction proceeded smoothly using $CeCl_3 \cdot 7H_2O$–NaI in refluxing acetonitrile under neutral conditions. The combination of cerium(III) chloride with NaI works efficiently to afford the corresponding 2-deoxyglycopyranosides in high yields (entries **a-l**, Table 1). However, in the absence of NaI, the glycals underwent Ferrier rearrangement under the influence of $CeCl_3 \cdot 7H_2O$ in refluxing acetonitrile to afford the corresponding 2,3-unsaturated hexopyranosides in good yields (Scheme 2).

In the absence of sodium iodide, the products were obtained as a mixture of α- and β-anomers, favoring the α-anomer. The ratios of products were determined by the examination of the ^1H NMR spectra of the crude products (entries **a-l**, Table 2). This clearly indicates that the addition of 1 equiv. of NaI is crucial to

Keywords: cerium reagents; D-glycals; 2-deoxysugars; carbohydrates.

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

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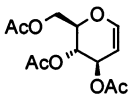
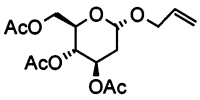
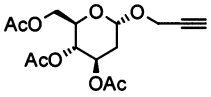
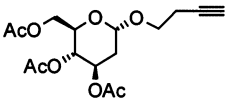
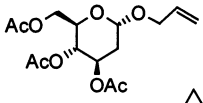
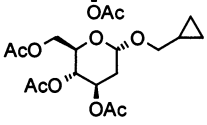
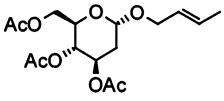
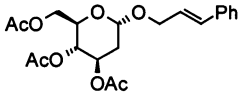
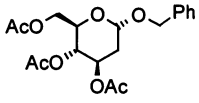
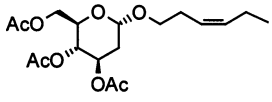
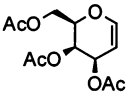
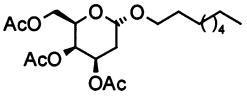
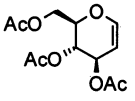
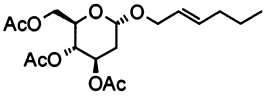
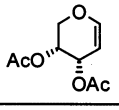
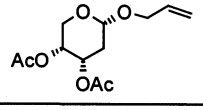
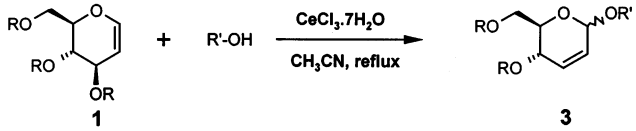
Table 1. $CeCl_3 \cdot 7H_2O$–NaI promoted synthesis of 2-deoxyglycopyranosides

Entry	Substrate 1	Product[a] 2	Time (h)	Yield (%)[b]
a			6.5	87
b	"		5.5	85
c	"		7.5	82
d	"		5.5	80
e	"		6.0	90
f	"		6.5	85
g	"		5.0	80
h	"		8.0	87
i	"		7.0	83
j			8.5	80
k			4.5	87
l			5.5	78

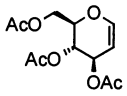
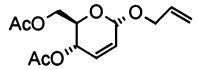
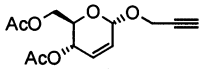
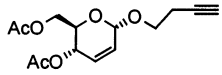
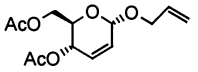
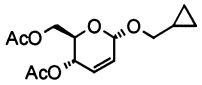
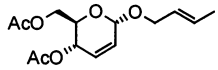
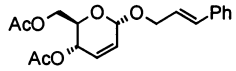
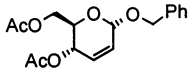
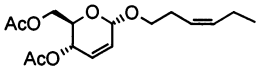
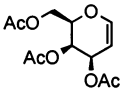
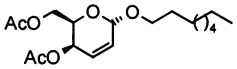
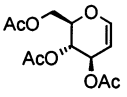
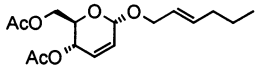
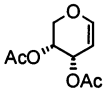
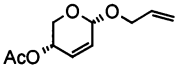
[a] All products were charcterized by ^1H, ^{13}C NMR, IR and mass spectroscopy
[b] Isolated and unoptimized yields

obtain 2-deoxyglycopyranosides. Furthermore, we have examined the possibility of $CeCl_3 \cdot 7H_2O$ functioning catalytically or at least, in less than stoichiometric amounts. But the best results were obtained with an equimolar ratio of $CeCl_3 \cdot 7H_2O$ and NaI. The scope and generality of this procedure is illustrated with respect to various glycals and alcohols. There are many advantages to the use of cerium(III) chloride for this transformation, which avoids the use of strongly acidic or basic conditions. The method does not require the use of expensive or corrosive reagents and no precautions need to be taken to exclude moisture from the reaction medium. Other glycals such as 3,4,6-tri-*O*-acetyl-D-galactal and 3,4-di-*O*-acetyl-D-xylal also reacted efficiently in high yields with high stereoselectivity. The



Scheme 2.

Table 2. $CeCl_3 \cdot 7H_2O$–NaI promoted synthesis of 2,3-unsaturated glycosides

Entry	Substrate 1	Product 3	Time (h)	Yields (%)[a]	Ratio[b] $\alpha : \beta$
a			7.5	85	9 : 1
b	"		8.0	78	7 : 3
c	"		8.5	85	7 : 3
d	"		9.0	83	9 : 1
e	"		7.0	88	8 : 2
f	"		7.5	85	9 : 1
g	"		8.0	80	6 : 4
h	"		9.0	82	6 : 4
i	"		10.0	78	7 : 3
j			9.5	75	8 : 2
k			8.5	83	8 : 2
l			6.5	87	9 : 1

a: Isolated and unoptimized yields
b: Anomeric ratios were determined on the basis of the integrated ratios of the anomeric hydrogens in the ^1H NMR spectra at 200 MHz

reaction probably proceeds through the activation of glycals by HI formed in situ from alcohols and sodium iodide in the presence of cerium(III) chloride to afford 2-deoxy products.[10]

In summary, this paper describes a mild and efficient method for the synthesis of 2-deoxyglycopyranosides from D-glycals and alcohols using $CeCl_3 \cdot 7H_2O$–NaI under neutral conditions, thereby leaving acid- and base-labile functional groups intact. The high levels of stereoselectivity in this process combined with a simple operation, high yields of products and ready availability of reagents at low cost will find wide use in organic synthesis.

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10. Experimental procedure: a mixture of 3,4,6-tri-*O*-acetyl-D-glucal (5 mmol), the alcohol (10 mmol), $CeCl_3 \cdot 7H_2O$ (7.5 mmol) and NaI (7.5 mmol) in acetonitrile (10 mL) was stirred at reflux temperature for a specified time as required to complete the reaction (Table 1). After complete conversion, as indicated by TLC, the reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate (2×15 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 the pure glycoside. Spectral data for the compounds: **2d** (Table 1): $[\alpha]_D^{20}$ (*α-anomer*) 124 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.87 (m, 1H, C=CH), 5.32–5.15 (m, 4H, H-3, H-4, C=CH_2), 5.04 (bd, 1H, J=3.0 Hz, H-1), 4.15 (m, 1H, H-5), 4.13 (m, 1H, -OCH), 4.07 (m, 2H, H-6a, 6b), 3.95 (m, 1H, -OCH), 2.11 (s, 3H, -$COCH_3$), 2.08 (m, 1H, H-2eq), 2.03 (s, 3H, -$COCH_3$), 1.96 (s, 3H, $COCH_3$), 1.88 (m, 1H, H-2ax). ^{13}C NMR (50 MHz): δ 20.5, 20.6, 30.1, 62.1, 66.1, 66.5, 66.7, 68.0, 96.0, 96.5, 117.3, 133.6, 169.5, 169.8, 169.9. EIMS: *m*/*z*: 330 M^+, 273, 213. IR (KBr) ν 3339, 3037, 1695, 1531, 1229, 978, 729 cm^{-1}.
2e (Table 1): $[\alpha]_D^{20}$ (*α-anomer*) 106 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.25 (m, 1H, H-3) 5.0 (brs, 1H, H-1), 4.90 (t, 1H, J=9.0 Hz, H-4), 4.20 (dd, 1H, J=4.5, 11.8, H-6a), 3.95 (m, 2H, H-6b, H-5), 3.35 (m, 2H, -OCH_2), 2.20 (dd, 1H, J=6.0, 13.5 Hz, H-2eq), 2.10 (s, 3H, -$COCH_3$), 2.08 (s, 3H, $COCH_3$), 1.98 (s, 3H, -$COCH_3$), 1.78 (ddd, 1H, J=6.0, 11.8, 13.5 Hz, H-2ax), 1.0 (m, 1H, -CH-), 0.5 (m, 2H, -CH_2-), 0.18 (m, 2H, -CH_2-). ^{13}C NMR (50 MHz): δ 2.9, 3.2, 10.3, 20.6, 20.9, 29.6, 35.1, 62.5, 67.8, 69.2, 69.7, 72.4, 96.5, 169.8, 170.0, 170.5. IR (KBr) ν: 3343, 3045, 1700, 1535, 1230, 970, 741 cm^{-1}.
3a (Table 2): solid, mp 42–43°C; $[\alpha]_D^{20}$ (*α-anomer*) 80.4 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.83–6.0 (m, 3H, H-2, H-3, H-2^1), 5.28–5.38 (m, 2H, H-4, H-3^{1}b), 5.22 (dq, J=10.4, 1H, H-3^{1}a), 5.08 (brs, 1H, H-1), 4.03–4.30 (m, 5H, H-5, H-6a, 6b, H-1^{1}a, 1^{1}b), 2.08 (s, 6H, $COCH_3$). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.7, 20.9, 62.9, 65.2, 66.9, 69.2, 93.6, 117.5, 127.7, 129.2, 134.0, 170.2, 170.7. IR (KBr) ν 3375, 2926, 1733, 1535, 1441 cm^{-1}.