Ceric(IV) ammonium nitrate-catalyzed glycosidation of glycals: a facile synthesis of 2,3-unsaturated glycosides

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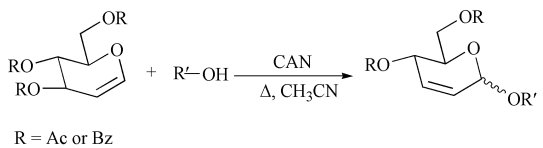
Glycosidation of glycals with alcohols in the presence of a catalytic amount of ceric(IV) ammonium nitrate under neutral conditions proceeds smoothly in refluxing acetonitrile to afford the corresponding 2,3-unsaturated glycosides in excellent yields.

2,3-Unsaturated glycosides are versatile chiral building blocks in the synthesis of several natural products.[1] 2,3- or 3-Deoxy sugars derived from 2,3-unsaturated glycosides are useful chiral intermediates in many bioactive molecules, such as antibiotics.[2] The acid-catalyzed allylic rearrangement of glycals in the presence of alcohols, known as the Ferrier rearrangement,[3] is widely employed to obtain 2,3-unsaturated glycosides. The reaction, as originally stated by Ferrier, involves the formation of a cyclic allylic oxocarbenium ion intermediate to which the nucleophile adds, preferentially in a quasi-axial orientation. A variety of reagents are employed to effect this transformation, including Lewis acids[4–6] as well as oxidants.[7] However, in spite of their potential utility, some of these methods involve stoichiometric amounts of catalysts, strongly acidic conditions, long reaction times, unsatisfactory yields and low diastereoselectivity. Therefore, the development of a neutral alternative would extend the scope of the useful *O*-glycosidation reaction.

In recent years, ceric(IV) ammonium nitrate (CAN) has attracted much attention as a catalyst in many carbon–carbon bond forming reactions.[8] It has also been widely used in carbon–heteroatom bond formation. CAN functions as a one-electron transfer catalyst in various organic transformations. However, glycosidation of glycals with alcohols under neutral conditions using ceric(IV) ammonium nitrate is unknown. Even though CAN has been used in the oxidative addition reactions of azides and malonates to glycals,[9] its use as a catalyst in *O*-glycosidation reactions has not been reported.

In continuation of our work on the glycosidation reactions of glycals,[10] we report here a mild and efficient procedure for the glycosidation (Scheme 1) of 3,4,6-tri-*O*-acetyl-D-glucal with various alcohols using ceric ammonium nitrate under neutral reaction conditions.

The treatment of 3,4,6-tri-*O*-acetyl-D-glucal with allyl alcohol in the presence of 10 mol% ceric ammonium nitrate in refluxing acetonitrile gave the corresponding *O*-allyl 2,3-unsaturated glycoside in 90% yield with high α-selectivity. Similarly, the reaction of primary, secondary, benzyl, cinnamyl, propargyl and aliphatic alcohols with tri-*O*-acetyl glucal in the presence of CAN proceeded smoothly in refluxing acetonitrile to give the respective *O*-glycosides in excellent yields with good α-anomeric selectivity. The predominant formation of the α-anomer may arise from the thermodynamic anomeric effect. However, the reaction of benzoylated glycals required longer reaction times (5–8 h), as well as higher loading of the catalyst (20% w/w of glycal), to achieve yields comparable with those of the acylated analogs. All the products were known in the literature and their charactization was easily achieved by ^{1}H, ^{13}C NMR and IR spectra after purification and also by comparison with authentic compounds. The results, as summarized in Table 1, reveal the scope and generality of the reaction with respect to various substituted alcohols.



R = Ac or Bz

R' = benzyl, allyl, propargyl, cinnamyl or alkyl

Scheme 1

Among the various solvents used for this transformation (tetrahydrofuran, dichloromethane, 1,4-dioxane and acetonitrile), CH_3CN was found to be superior in terms of yields and reaction time due to the high solubility of CAN in acetonitrile. The glycosidation of glycal with an alcohol in the presence of CAN may proceed through a one-electron transfer with initial formation of a radical cation and an allylic oxonium intermediate, as shown in Scheme 2.

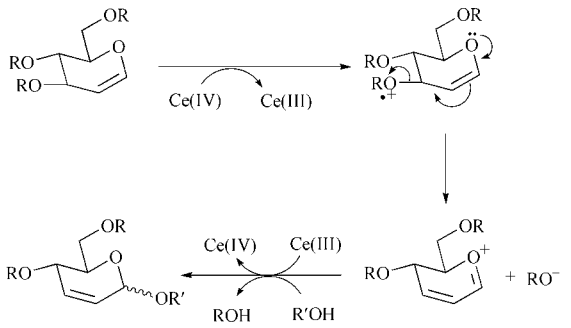
In conclusion, ceric(IV) ammonium nitrate has been demonstrated to be an efficient and mild catalyst for the Ferrier glycosidation of glycals with a variety of alcohols under neutral conditions. Due to the neutral reaction conditions, this method may find applications in the glycosidation of acid-sensitive substrates.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz instrument using TMS as an internal reference. IR spectra were recorded on a Perkin–Elmer FT-IR spectrophotometer. Thin layer chromatography (TLC) was performed on silica gel Merck 60 F_{254} precoated plates.

General procedure for the *O*-glycosidation of glycals

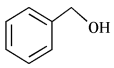
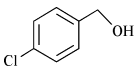
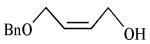
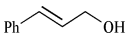
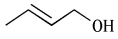
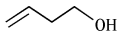
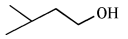
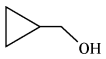
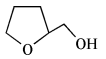
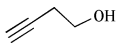
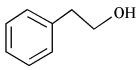
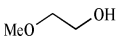
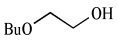
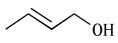
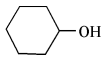
A mixture of 3,4,6-tri-*O*-acetyl-D-glucal (5 mmol) or 3,4,6-tri-*O*-benzoyl-D-glucal (5 mmol), alcohol (7 mmol) and ceric



Scheme 2

 DOI: 10.1039/b009973m

Table 1 Ceric ammonium nitrate-catalyzed *O*-glycosidation of tri-*O*-acetyl- or tri-*O*-benzoyl-D-glucal[a]

Entry	Glucal R[b]	Alcohol R′OH[b]	Reaction time/h	Yield[c] (%)	Anomeric ratio[d] α : β
a	Ac		3.0	90	7 : 1
b	Ac		3.5	92	7 : 1
c	Ac		4.0	87	8 : 2
d	Ac		2.5	89	9 : 1
e	Bz		7.0	80	10 : 1
f	Bz		6.0	80	8 : 2
g	Ac		3.0	92	8 : 2
h	Ac		3.5	81	14 : 1
i	Ac		3.0	90	14 : 1
j	Ac		4.0	82	8 : 2
k	Ac		2.5	90	8 : 2
l	Ac		4.5	87	12 : 1
m	Bz		8.0	87	8 : 2
n	Ac		4.5	85	7 : 2
o	Ac		3.0	90	8 : 2
p	Ac		4.0	85	7 : 2
q	Ac		3.0	90	10 : 1
r	Ac		4.5	80	14 : 1
s	Ac	Cholesterol	5.0	78	10 : 1

[a] All the products were characterized by ^{1}H and ^{13}C NMR and IR spectra. [b] Bn = benzyl; Bz = benzoyl; Bu = *n*-butyl. [c] Isolated yields as anomeric mixtures after purification. [d] The anomeric ratio was determined on the basis of the integrated ratios of the anomeric hydrogens in the ^{1}H NMR spectra.

ammonium nitrate (0.5 mmol) in acetonitrile (15 ml) was stirred under reflux for the appropriate time (see Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was quenched with water (10 ml) and extracted with ethyl acetate (2 × 15 ml). The combined 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 2 : 8) to afford pure 2,3-unsaturated glycosides. Representative spectroscopic data are given below.

Entry i. *α-isomer*: liquid, ^{1}H NMR ($CDCl_3$): δ 0.20 (m, 2H), 0.55 (m, 2H), 1.05 (m, 1H), 2.05 (s, 6H), 3.45 (m, 2H), 4.05 (m, 1H, 5-H), 4.15 (m, 2H, 6-H_a, 6-H_b), 5.05 (br s, 1H, 4-H), 5.25 (d, 1H, J = 8.50 Hz, 1-H), 5.85 (m, 2H, 2-H, 3-H). ^{13}C NMR (proton decoupled, $CDCl_3$): δ 2.9, 3.2, 10.4, 20.5, 20.7, 62.8, 65.1, 66.7, 72.5, 73.1, 93.6, 127.8, 128.8, 169.9, 170.3. IR (KBr): ν 3469, 3378, 3007, 2907, 2358, 1744, 1374, 1235, 1039, 907, 830 cm^{-1}. *β-isomer*: liquid, ^{1}H NMR ($CDCl_3$): δ 0.20 (m, 2H), 0.55 (m, 2H), 1.05 (m, 1H), 2.05 (s, 6H), 3.45 (m, 2H), 4.10 (m, 1H, 5-H), 4.20 (m, 2H, 6-H_a, 6-H_b), 5.10 (br s, 1H, 4-H), 5.25 (d, 1H, J = 8.50 Hz, 1-H), 5.90 (m, 2H, 2-H, 3-H).

Entry k. *α-isomer*: liquid, ^{1}H NMR ($CDCl_3$): δ 1.90 (s, 1H), 2.05 (s, 6H), 2.50 (m, 2H), 3.65 (m, 1H), 3.85 (m, 1H), 4.10 (m, 1H, 5-H), 4.15 (m, 2H, 6-H_a, 6-H_b), 5.00 (br s, 1H, 4-H), 5.25 (d, 1H, J = 8.5, 1-H), 5.85 (dd, 2H, J = 10.3 and 4.7 Hz, 2-H, 3-H). ^{13}C NMR (proton decoupled, $CDCl_3$): δ 19.9, 20.6, 20.8, 62.7, 65.0, 66.7, 66.9, 69.3, 80.9, 94.4, 127.3, 129.2, 170.1, 170.6. IR (KBr): ν 3468, 3286, 2926, 2121, 1739, 1373, 1232, 1042, 907, 733 cm^{-1}. *β-isomer*: liquid, ^{1}H NMR ($CDCl_3$): δ 1.90 (s, 1H), 2.05 (s, 6H), 2.50 (m, 2H), 3.65 (m, 1H), 3.85 (m, 1H), 4.13 (m, 1H, 5-H), 4.20 (m, 2H, 6-H_a, 6-H_b), 5.10 (br s, 1H, 4-H), 5.25 (d, 1H, J = 8.5, 1-H), 5.95 (dd, 2H, J = 10.3 and 4.7 Hz, 2-H, 3-H).

Entry n. *α-isomer*: liquid, ^{1}H NMR ($CDCl_3$): δ 2.05 (s, 6H), 3.35 (s, 3H), 3.55 (t, 2H, J = 6.8), 3.65 (m, 1H), 3.85 (m, 1H), 4.05 (m, 1H, 5-H), 4.20 (m, 2H, 6-H_a, 6-H_b), 5.0 (br s, 1H, 4-H), 5.30 (d, 1H, J = 8.5, 1-H), 5.85 (dd, 2H, J = 10.7 and 5.0 Hz, 2-H, 3-H). ^{13}C NMR (proton decoupled, $CDCl_3$): δ 20.5, 20.7, 58.7, 62.8, 65.2, 66.8, 67.5, 71.6, 94.4, 127.6, 129.0, 130.2, 170.0, 172.2. IR (KBr): ν 3469, 2929, 1741, 1373, 1234, 1047, 904, 735 cm^{-1}. *β-isomer*: liquid, ^{1}H NMR ($CDCl_3$): δ 2.05 (s, 6H), 3.35 (s, 3H), 3.55 (t, 2H, J = 6.8), 3.65 (m, 1H), 3.85 (m, 1H), 4.10 (m, 1H, 5-H), 4.25 (m, 2H, 6-H_a, 6-H_b), 5.10 (br s, 1H, 4-H), 5.30 (d, 1H, J = 8.5, 1-H), 5.95 (dd, 2H, J = 10.7 and 5.0 Hz, 2-H, 3-H).

Entry q. *α-isomer*: liquid, ^{1}H NMR ($CDCl_3$): δ 1.75 (d, 3H, J = 6.8), 2.05 (s, 6H), 3.95 (m, 2H), 4.05 (m, 1H, 5-H), 4.15 (m, 2H, 6-H_a, 6-H_b), 5.00 (br s, 1H, 4-H), 5.25 (d, 1H, J = 8.5, 1-H),

5.60 (m, 1H), 5.70 (m, 1H), 5.85 (dd, 2H, $J = 10.5$ and 4.8 Hz, 2-H, 3-H). ^{13}C NMR (proton decoupled, $CDCl_3$): δ 17.5, 20.5, 20.7, 62.8, 63.3, 65.2, 66.7, 68.7, 93.1, 126.7, 127.7, 128.9, 130.0, 130.4, 169.9, 170.4. IR (KBr): ν 3471, 3379, 2920, 2361, 1745, 1546, 1451, 1371, 1232, 1186, 1034, 968, 908, 732 cm^{-1}. *β-isomer*: liquid, ^1H NMR ($CDCl_3$): δ 1.75 (d, 3H, $J = 6.8$), 2.05 (s, 6H), 3.95 (m, 2H), 4.10 (m, 1H, 5-H), 4.25 (m, 2H, 6-H_a, 6-H_b), 5.10 (br s, 1H, 4-H), 5.25 (d, 1H, $J = 8.5$, 1-H), 5.60 (m, 1H), 5.70 (m, 1H), 5.90 (dd, 2H, $J = 10.5$ and 4.8 Hz, 2-H, 3-H).

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