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Molecular iodine-promoted N- and C-glycosylation of 1-*C*-alkyl (or phenyl)-glycopyranoses

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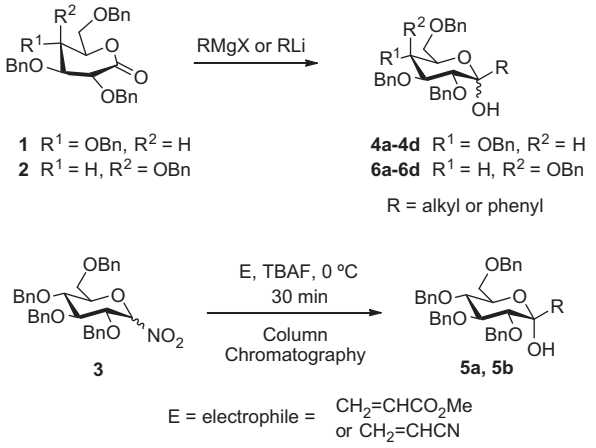
ABSTRACT

Molecular iodine efficiently promoted the N- and C-glycosylation of hemiketals with Me_3SiN_3 and Me_3SiCN, respectively. Using this method we have prepared diverse functional *N*- and *C*-ketosides, which could serve as useful synthons for the preparation of unnatural glycosyl amino acids or glycopeptides.

Synthetic manipulations at the anomeric center lead to useful and interesting transformations in carbohydrate chemistry.[1] Among the reactions at the anomeric center, particularly, O-, C- and N-glycosylations[2–4] have gained significant importance in the field of carbohydrate chemistry and biochemistry. Recently, *C*-glycosides have received much attention from the biological and synthetic standpoints. These are the stable mimics of naturally occurring *O*- and *N*-glycosides. Consequently, this class of compounds is currently receiving much interest because of their biological activity and these are potent antitumor, antiviral, or antibiotic agents.[5] Therefore, various effective methods have been reported for the stereoselective synthesis of *C*-glycosides.[6]

Further, 1-*C*-alkyl-sugars, also called as artificial ketoses, or hemiketals, are a novel class of *C*-glycosides having an alkyl group at the anomeric center, which mimics naturally occurring aldoses and have also gained considerable importance[7–9] in synthetic carbohydrate chemistry. The O- or C- or N-glycosylation of these 1-*C*-alkyl-sugars leads to 1-*C*-alkyl-glycosides, also called as *O*- or *C*- or *N*-ketosides,[7–9] which are considered as a new class of *C*-glycoside analogs and these are expected to possess biological activities different from those of natural molecules[9a,10] and thus allow the structure-activity relationship to be studied. Because of their pharmacological importance, together with the diverse structural features, several groups are currently working to develop the chemistry of 1-*C*-alkyl-sugars.[11]

For the past few years, we have been interested in developing newer methodologies for functionalizing 2,3-glycals[4a,b,12] and their derivatives en route to some useful carbohydrate synthons. More recently, we have developed a method for the direct conversion of unstable amino precursors viz. 1-*C*-alkyl-1-nitro sugars into stable amino precursors viz. 1-*C*-alkyl-1-azido sugars.[13] This methodology gave an easy access for the synthesis of 6,5-fused spiroaminals (fused *N*-ketosides), which are moderate glycosidase inhibitors. In continuation of our interest in exploring the chemical and biological properties of ketosides,[13] we hereby report on



Scheme 1. Preparation of hemiketals from δ-lactones **1**, **2** and 1-nitro sugar **3**.

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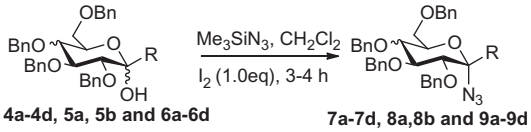
N- and C-glycosylation of 1-*C*-alkyl-sugars using molecular iodine as a promoter.

Usually glycosylation of 1-*C*-alkyl-sugars is carried out using few Lewis acids such as $BF_3{\cdot}OEt_2$,[11f] $Sc(OTf)_3$,[7d] and Me_3SiOTf.[11g] However, some of these reagents are associated with drawbacks such as high cost, corrosive nature, moisture sensitive, toxic, and difficulty in handling. Therefore, the development of simple, efficient, and inexpensive reagents, which can provide convenient procedures with good yields, is necessary. Recently, molecular iodine has gained considerable attention as an inexpensive, non-toxic, nonmetallic, and readily available Lewis acid catalyst for effecting various carbohydrate[14] as well as non-carbohydrate[15] organic transformations. Herein, we wish to report a simple and efficient method for the preparation of *N*- and *C*-ketosides using molecular iodine as promoter.

For the synthesis of 1-*C*-alkyl-sugars we have chosen D-glucono-1-5-loctone **1**, D-galactono-1-5-lactone **2**, and glucose derived 1-nitro sugar **3** as the starting materials. The addition reaction of organometallic reagent (RMgX or RLi) to lactones **1** and **2** produced hemiketals **4a–d**[11g,16] and **6a–d**,[6d,16] respectively (Scheme 1). The

Table 1
Azidation of hemiketals in the presence of $TMSN_3$ and I_2 (−40 °C to rt)



4a-4d, 5a, 5b and 6a-6d **7a-7d, 8a,8b and 9a-9d**

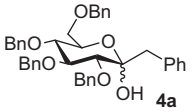
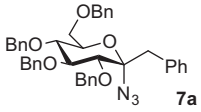
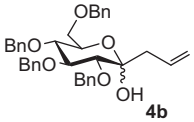
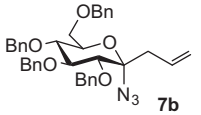
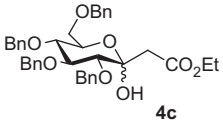
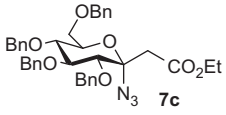
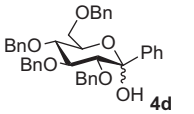
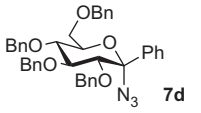
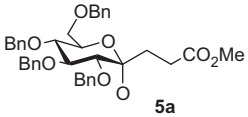
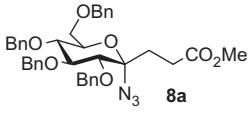
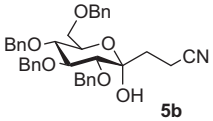
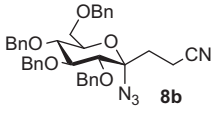
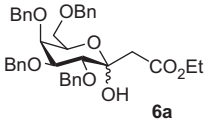
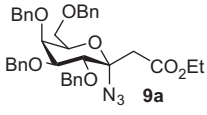
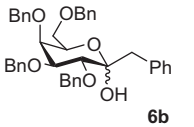
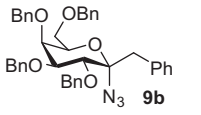
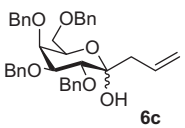
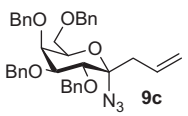
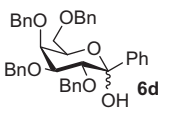
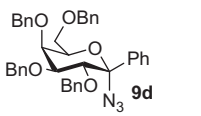
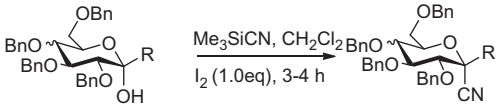
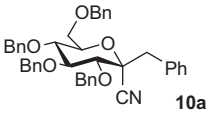
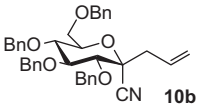
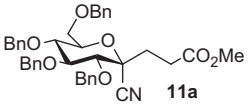
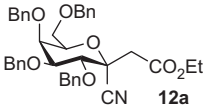
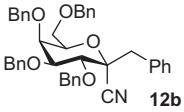
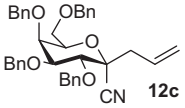
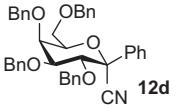
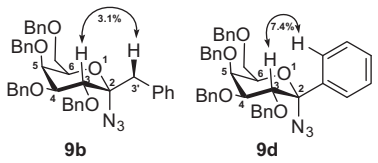
Entry	Hemiketals	*N*-Ketaosides	Yield (%)
1	 **4a**	 **7a**	79[11g]
2	 **4b**	 **7b**	75[11g]
3	 **4c**	 **7c**	89
4	 **4d**	 **7d**	77[11g]
5	 **5a**	 **8a**	80[13]
6	 **5b**	 **8b**	73[13]
7	 **6a**	 **9a**	95
8	 **6b**	 **9b**	76
9	 **6c**	 **9c**	72
10	 **6d**	 **9d**	96

Table 2
Cyanation of hemiketals in the presence of TMSCN and I_2 (−40 °C to rt)



4a, 4b, 5a and 6a-6d **10a, 10b, 11a and 12a-12d**

Entry	Hemiketals	*C*-Ketosides	Yield (%)
1	**4a**	 **10a**	67[11g]
2	**4b**	 **10b**	63[11g]
3	**5a**	 **11a**	93
4	**6a**	 **12a**	71
5	**6b**	 **12b**	65
6	**6c**	 **12c**	69
7	**6d**	 **12d**	84



9b **9d**

Figure 1. NOE correlations of compound **9b** and **9d**.

other glucose derived hemiketals **5a** and **5b** were prepared by utilizing the chemistry of anomeric nitro sugar **3**. Thus, reaction of nitro sugar **3** with methyl acrylate or acrylonitrile in the presence of a catalytic amount of *n*-tetrabutylammonium fluoride (TBAF) at 0 °C gave hemiketal **5a** or **5b**.[13]

As a preliminary study hemiketal **4a** was treated with azidotrimethylsilane (Me_3SiN_3) in CH_2Cl_2 in the presence of molecular iodine. The reaction proceeded smoothly at room temperature and afforded the desired glycosyl azide **7a**[11g] as a single isomer in good yield (Table 1). Best results were obtained by using 1 equiv of molecular iodine in CH_2Cl_2 at −40 °C to room temperature. Reduction in catalyst loading was ineffective as it led to longer reaction time and lowering of chemical yield. Similarly, the glucose derived hemiketals **4b–d** and the galactose derived hemiketals **6a–d** reacted smoothly to afford glycosyl azides **7b–d**[11g] and **9a–d** in good yield. The 1-nitro sugar derived hemiketals **5a** and **5b** also produced azido ester **8a** and azido cyanide **8b** in 80% and 73% yield, respectively[13] (Table 1).

The optimized reaction conditions were also effective for the cyanation of 1-*C*-alkyl-sugars. Thus, the treatment of 1-nitro sugar derived hemiketal **5a** with Me_3SiCN in the presence of 1 equiv of molecular iodine in CH_2Cl_2 under similar conditions produced cyano-ester **11a** (Table 2) in excellent yield (93%), which could serve as a novel, useful synthon for the preparation of artificial glycopeptides.[17] The formation of the product was confirmed through its spectral data. Thus, ^{1}H NMR spectrum of compound **11a** showed a characteristic peak of –OMe at δ 3.65 as a singlet and ^{13}C NMR spectrum showed the CN group carbon peak at δ 116.8. Further, hemiketals **4a**, **4b** and **6a–d** also furnished glycosyl cyanides **10a**, **10b**,[11g] and **12a–d** in good to moderate yields.[18]

Interestingly, all the products were obtained as single isomers viz. α-isomers. This is not surprising as in similar types of Lewis acid catalyzed glycosylations of glucose derived ketoses, formation of a single α-isomer has been well demonstrated in the literature.[11g,13] In the case of galactose series, the configuration at the anomeric center was established based on NOE experiments (Fig. 1). In ketoside **9b** irradiation of H-3′ methylene proton at δ 3.18 enhanced the signal for H-3 proton at δ 3.89 (3.1% NOE) and did not enhance the signal for H-4 proton at δ 3.94, clearly indicating that the azide group occupies the axial position. In the case of phenyl ketoside **9d**, irradiation of *ortho* protons at δ 7.65 enhanced the signal for H-3 proton at δ 3.92 (7.4% NOE) also clearly indicating the formation of axial azide. Similarly NOE was observed between H-3 and H-3′ protons of compound **12b** (see Supplementary data). We have also further confirmed the axial orientation of cyanide moiety in galactose derived ketosides from the single-crystal X-ray data[19] of compound **12d**.

In conclusion, we have developed a simple, inexpensive, and efficient method for providing α-*N*- and *C*-ketosides using molecular iodine as promoter. The procedure is experimentally simple and using this method we prepared diverse functional glycosyl azides and cyanides, which are useful synthons for the synthesis of peptide mimetics.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.124.

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18. *Experimental data of selected compounds*: General procedure for N- and C-glycosylation of 1-*C*-alkyl-sugars: To a stirred solution of hemiketal (0.07 mmol) in 1.0 mL dry dichloromethane, iodine (0.07 mmol, dissolved in 0.5 mL CH_2Cl_2) was added. To this reaction mixture $TMSN_3$ or TMSCN (0.21 mmol) was added slowly dropwise at −40 °C and allowed to stir at room temperature for 3–4 h. After complete conversion as indicated by TLC, the reaction mixture was quenched with 15% solution of sodium thiosulfate (1.5 mL) and extracted with dichloromethane (2 × 15 mL). The combined extracts was concentrated in vacuo. The resulting product was purified by column chromatography on silica gel to afford the pure *N*- or *C*-ketoside.
(2S,3R,4S,5S,6R)-2-Allyl-2-azido-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran (**9c**): R_f: 0.65 (hexane/ethyl acetate, 9:1) Oil. Yield: 72% $[\alpha]_D^{28}$ +72.65 (*c* 0.89, CH_2Cl_2). IR (neat) ν_{max}: 2114, 1596, 1385, 1362 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.36–7.25 (m, 20H, *Ar-H*), 5.94–5.89 (m, 1H, –*CH*═CH_2), 5.18–5.14 (m, 2H, –CH═*CH*$_2$), 4.98 (d, 1H, *J* = 10.9 Hz, PhC*H*), 4.97 (d, 1H, *J* = 11.7 Hz, PhC*H*), 4.75–4.68 (m, 3H, 3 × PhC*H*), 4.60 (d, 1H, *J* = 11.6 Hz, PhC*H*), 4.51 (d, 1H, *J* = 12.0 Hz, PhC*H*), 4.45 (d, 1H, *J* = 11.7 Hz, PhC*H*), 4.03–3.99 (m, 3H), 3.92 (dd, 1H, *J* = 2.7, 9.6 Hz), 3.62 (dd, 1H, *J* = 7.5, 9.3 Hz), 3.56 (dd, 1H, *J* = 5.5, 9.3 Hz), 2.80 (dd, 1H, *J* = 6.5, 14.4 Hz, -CH_aH_bCH═CH_2), 2.70 (dd, 1H, *J* = 7.5, 14.4 Hz, CH_aH_bCH═CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.9, 138.3, 138.0, 131.6, 128.5–127.6 (m, *Ar-C*), 119.5, 94.4, 81.2, 78.4, 75.6, 74.5, 74.1, 73.6, 72.7, 72.3, 68.5, 40.3. HRMS calcd for $C_{37}H_{39}N_3O_5$ $[M + NH_4]^+$ 623.3233, Found: 623.3234.
(2S,3R,4S,5S,6R)-2-Azido-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-2-phenyltetrahydro-2H-pyran (**9d**): R_f: 0.7 (hexane/ethyl acetate, 9:1) Oil. Yield: 96% $[\alpha]_D^{28}$ +2.16 (*c* 0.925, CH_2Cl_2). IR (neat) ν_{max}: 2918, 2111, 1590, 1097 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, 2H, *J* = 6.9 Hz, *Ar-H*), 7.41–7.19 (m, 21H, *Ar-H*), 7.03–7.02 (m, 2H, *Ar-H*), 4.99 (d, 1H, *J* = 11.4 Hz, PhC*H*), 4.78–4.72 (ABq, 2H, *J* = 11.7 Hz, PhCH_2), 4.63 (d, 1H, *J* = 11.4 Hz, PhC*H*), 4.53 (d, 1H, *J* = 11.4 Hz, PhC*H*), 4.49–4.45 (m, 2H, 2 × PhC*H*), 4.25–4.23 (m, 1H, *H-6*), 4.10 (br s, 1H, *H-5*), 3.96 (dd, 1H, *J* = 2.7, 10.1 Hz, *H-4*), 3.92 (d, 1H, *J* = 9.6 Hz, *H-3*), 3.89 (d, 1H, *J* = 10.5 Hz, PhC*H*) 3.80 (dd, 1H, *J* = 7.8, 8.8 Hz), 3.69 (dd, 1H, *J* = 5.5, 9.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.9, 138.8, 138.4, 137.8, 137.4, 128.7–126.9 (m, *Ar-C*), 96.3, 80.7, 75.9, 75.8, 74.9, 74.8, 73.5, 73.0, 72.7, 68.5. HRMS calcd for $C_{40}H_{39}N_3O_5$ $[M+Na]^+$ 664.2787, found: 664.2787.
Methyl3-((2R,3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-2-cyanotetrahydro-2H-pyran-2-yl) propanoate (**11a**): R_f: 0.5 (hexane/ethyl acetate, 4:1) Oil. Yield: 93% $[\alpha]_D^{28}$ +29.19 (*c* 0.605, CH_2Cl_2). IR (neat) ν_{max}: 2919, 1739, 1598, 1496, 1092 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.17 (m, 20H, *Ar-H*), 4.94 (d, 1H, *J* = 11.2 Hz, PhC*H*), 4.91–4.84 (m, 2H, PhCH_2), 4.79 (d, 1H, *J* = 11.7 Hz, PhC*H*), 4.73 (d, 1H, *J* = 11.2 Hz, PhC*H*), 4.61–4.54 (m, 2H, 2 × PhC*H*), 4.48 (d, 1H, *J* = 12.2 Hz, PhC*H*), 3.93 (t, 1H, *J* = 9.2 Hz), 3.82–3.64 (m, 4H), 3.65 (s, 3H, OCH_3), 3.35 (d, 1H, *J* = 9.5 Hz), 2.55–2.51 (m, 2H), 2.40–2.33 (m, 1H), 1.99–1.92 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.7, 138.1, 137.9, 137.8, 137.2, 128.6–127.9 (m, *Ar-C*), 116.8, 84.6, 81.1, 77.9, 76.9, 76.7, 75.9, 75.6, 75.2, 73.5, 68.1, 51.9, 31.8, 28.5. HRMS calcd for $C_{39}H_{41}NO_7$ $[M+H]^+$ 636.2961, found: 636.2963.
(2R,3R,4S,5S,6R)-2-Benzyl-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-carbonitrile (**12b**): R_f: 0.7 (hexane/ethyl acetate, 4:1) Oil. Yield: 65% $[\alpha]_D^{28}$ +18.88 (*c* 0.3, CH_2Cl_2). IR (neat) ν_{max}: 2924, 1496, 1454, 1265, 1101 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.36–7.23 (m, 25H, *Ar-H*), 5.04 (d, 1H, *J* = 11.7 Hz, PhC*H*), 4.91 (d, 1H, *J* = 11.5 Hz, PhC*H*), 4.75–4.67 (m, 3H, 3 × PhC*H*), 4.56 (d, 1H, *J* = 11.4 Hz, PhC*H*), 4.44–4.41 (ABq, 2H, *J* = 11.7 Hz, 2 × PhC*H*), 4.04–4.03 (m, 1H, *H-5*), 3.97–3.94 (m, 1H, *H-6*), 3.92 (dd, 1H, *J* = 2.6, 9.75 Hz, *H-4*), 3.84 (d, 1H, *J* = 9.7 Hz, *H-3*), 3.63 (dd, 1H, *J* = 7.75, 9.45 Hz, CH_aH_bOBn), 3.55 (dd, 1H, *J* = 5.4, 9.2 Hz, CH_aH_bOBn), 3.25 (d, 1H, *J* = 14.0 Hz, CH_aH_bPh)), 2.98 (d, 1H, *J* = 14.3 Hz, CH_aH_bPh)). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.6, 138.0, 137.9, 134.1, 130.9, 128.6–127.4 (m, *Ar-C*), 117.3, 82.5, 79.8, 75.4, 74.9, 74.7, 73.5, 72.8, 68.1, 42.2. HRMS calcd for $C_{42}H_{41}NO_5$ $[M+H]^+$ 640.6063, found: 640.6063.
19. CCDC 784656 (for **12d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.