Amidochlorination of 4-*O*-Azidoformyl-D-pseudoglycals with Iron (II) Chloride and Chlorotrimethylsilane†

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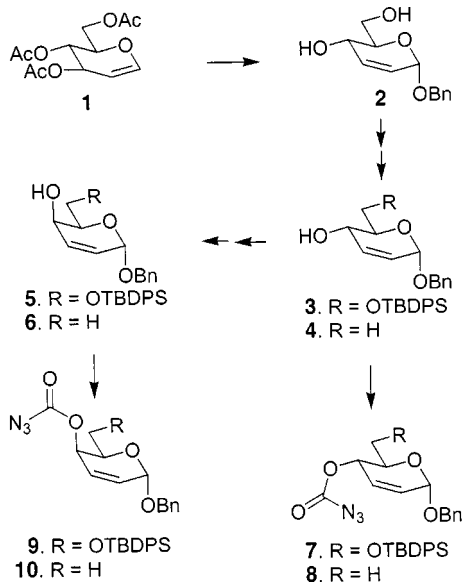
Intramolecular photolysis or thermolysis of simple allylic azidoformates affords aziridine derivatives which further rearrange to the ring-opened products or react with nucleophiles to produce 1,3-oxazolidin-2-one derivatives.[1-5] Intramolecular thermolysis of azidoformate group with an olefin produces aziridine derivatives[6] and intermolecular photolysis of ethyl azidoformate with an olefin in the presence of a trace of water affords 1,2-amidoalcohols.[7] Intramolecular photocycloaddition of carbamoyl azide and an olefin also affords aziridine derivatives.[8]

Application of these inter- or intramolecular photolysis reactions to D-glycals has also been reported. Intramolecular photolysis of 3-*O*-azidoformyl-4,6-*O*-isopropylidene-D-allal in alcohol affords 2-amido-2-deoxy-D-allopyranosides in regio and stereoselective manner.[9,10] Intermolecular photolysis of D-glucal or D-galactal derivatives with ethyl azidoformate in alcohol also produces 2-amido-2-deoxy-D-glycopyranosides.[11,12]

Reaction of simple allylic azidoformates with 0.1 equivalents of iron (II) chloride and 1.5 equivalents of chlorotrimethylsilane (TMSCl) in ethanol is known to produce 4-chloroalkyl-1,3-oxazolidin-2-one derivatives in moderate yield.[13] We intended to apply this methodology to the various unsaturated monosaccharides having allylic alcohol moiety because monosaccharides having amino or nitro groups at 2-, 3-, 4-, or 6-position are important structural components of the glycopeptide antibiotics.[14] Herein we report the synthesis of cyclic carbamates of 3-amino-2-chloro-2,3-dideoxy-D-glycopyranosides from D-pseudoglycals (2,3-dideoxy-D-*threo*(or *erythro*)-hex-2-enopyranosides) with iron (II) chloride and TMSCl.

Results and Discussion

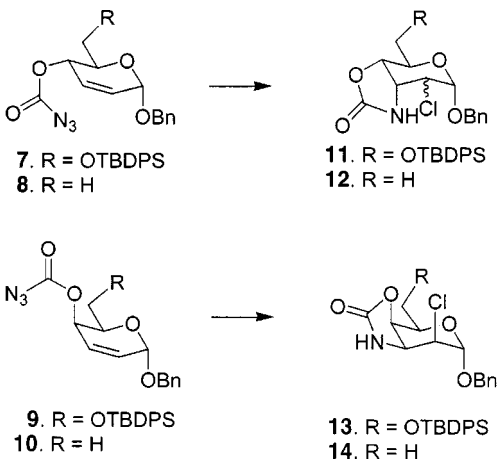
Tri-*O*-acetyl-D-glucal (**1**) was Ferrier-transformed[15] and deacetylated to give benzyl α-D-pseudoglucal (**2**). Selective protection of the 6-hydroxyl group of **2** with *t*-butyldiphenylsilyl chloride (TBDPSCl) produced compound **3**. Monotosylation of the 6-hydroxyl group of **2** followed by the reduction with lithium aluminumhydride afforded 6-deoxy compound **4**. Inversion of the configuration of the 4-hydroxyl group of **3** and **4** by Mitsunobu method[16] with



Scheme 1. Preparation of D-pseudoglycals.

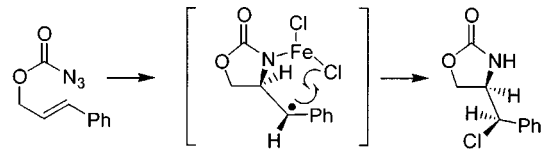
benzoic acid and hydrolytic debenzolyation produced benzyl α-D-pseudogalactal derivatives **5** and **6**. Treatment of these allylic alcohol derivatives **3**, **4**, **5**, and **6** with 4-nitrophenyl chloroformate and pyridine followed by sodium azide[2] afforded the corresponding benzyl 4-*O*-azidoformyl-α-D-pseudoglycals **7**, **8**, **9**, and **10** in 69, 75, 85, and 84 % yield, respectively (Scheme 1).

These 4-*O*-azidoformyl-D-pseudoglycals **7**, **8**, **9**, and **10**



Scheme 2. Amidochlorination reactions

†This paper is dedicated to the late Professor Sang Chul Shim with respect - a remarkable gentleman and a truly exceptional scientist.



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Scheme 3. Radical intermediate for *syn* addition.

were treated with 0.1 equivalents of iron (II) chloride and 1.5 equivalents of TMSCl in ethanol for 20 hr at room temperature and the reaction mixture was worked up by usual manner and purified by column chromatography on silica gel to give cyclic carbamates of 3-amino-2-chloro-α-D-glycopyranosides **11**, **12**, **13**, and **14** in 30, 32, 30, and 52% yield, respectively. Some of starting materials were recovered in most cases, and byproducts such as 4-*O*-carbamoyl derivatives and 6-hydroxyl compounds were also obtained (Scheme 2).

The stereochemical outcome of this amidochlorination reaction is not fully understood, but T. Bach *et al*. proposed[13] the radical intermediate **15** for the reaction of 3-phenyl-2-propenyl azidoformate with iron (II) chloride and TMSCl, and thus the *syn* addition of amido group and chlorine to the double bond could be obtained (Scheme 3). In our 4-*O*-azidoformyl derivatives, the configuration of the 4-position could play an important role for the stereochemical outcome during this addition reaction. In case of **7** and **8**, amido group and chlorine should approach to the double bond from the down face and in case of **9** and **10** from the upper face, respectively. However, ^{1}H-NMR studies show that in case of **11** and **12**, 2-epimers were obtained in a ratio of 8:3, whereas in case of **13** and **14**, single isomers were isolated. These assignments were supported unambiguously by ^{1}H-NMR spectrum of **13** which exhibited coupling constants, $J_{1,2}$ = 6 Hz, $J_{2,3}$ = 3 Hz, and $J_{3,4}$ = 9 Hz, in good agreement with cyclic carbamate of benzyl 3-amino-2-chloro-6-*O*-(*t*-butyldiphenylsilyl)-2,3-dideoxy-α-D-talopyranoside.[17]

Even though this amidochlorination method gives rise to the low to moderate yields, it is quite simple and predictable compared to conventional photolysis or thermolysis. We are trying to identify the new horizon of this method by replacing iron (II) chloride with iron (II) bromide and the new amidobromination reaction of same substrates is in progress.

Experimental Section

The representative experimental procedures for the preparation of 4-*O*-azidoformyl derivatives and their amidochlorination reactions are as follows.

Benzyl 4-*O*-azidoformyl-6-*O*-(*t*-butyldiphenylsilyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (7). To a stirred solution of benzyl 6-*O*-(*t*-butyldiphenylsilyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**3**, 0.75 g, 1.58 mmol) and pyridine in benzene (10 mL) was added 4-nitrophenyl chloroformate (0.64 g, 3.16 mmol) and the solution was stirred for 2.5 hr at rt. Ethyl acetate (20 mL) was added followed by aqueous sodium bicarbonate solution and the organic layer was separated. Usual workup and evaporation gave yellow solid which was dissolved in DMF (6 mL) without further purification. Sodium azide (1.03 g, 15.8 mmol) was added and the solution was stirred for 19 hr at 35 ^{o}C. Aqueous ammonium chloride solution was added followed by chloroform and the organic layer was purified. Column chromatography of the crude syrup afforded colorless oily product in 69% yield (0.59 g, 1.09 mmol). IR (cm^{-1}): 2191, 2120 (azide), 1728 (carbonyl). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 7.72-7.60 (m, 4H), 7.44-7.23 (m, 11H), 5.96-5.88 (m, 2H, H-2 and H-3), 5.40 (d, J = 9 Hz, H-1), 5.13 (s, 1H, H-4), 4.79 (d, J = 12 Hz, 1H, benzylic H), 4.59 (d, J = 12 Hz, 1H, benzylic H), 4.10-4.02 (m, 1H, H-5), 3.79-3.76 (m, 2H, H-6), 1.07 (s, 9H, *t*-butyl).

Cyclic carbamate of benzyl 3-amino-2-chloro-6-*O*-(*t*-butyldiphenylsilyl)-2,3-dideoxy-α-D-talopyranoside (13). A solution of benzyl 4-*O*-azidoformyl-6-*O*-(*t*-butyldiphenylsilyl)-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside (**9**, 0.33 g, 0.60 mmol) in ethanol (10 mL) was degassed with argon and cooled to 0 ^{o}C. Chlorotrimethylsilane (0.11 mL, 0.90 mmol) and iron (II) chloride (7.6 mg, 0.06 mmol) were added and the solution was stirred for 20 hr at rt. A small amount of water was added, ethanol was evaporated and the residue was extracted with ethyl acetate. Usual workup and column chromatography afforded an oily product in 30% yield (0.10 g, 0.18 mmol). IR (cm^{-1}): 3614 (brd, NH), 1769 (carbonyl), 1738 (carbonyl), 1465. ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 7.68-7.64 (m, 4H), 7.44-7.36 (m, 6H), 7.29 (s, 5H), 5.59 (brd d, 1H, D_2O exchangeable, NH), 4.90 (d, J = 6 Hz, 1H, H-1), 4.89 (d, J = 9 Hz, 1H, H-4), 4.75 (d, J = 12 Hz, 1H, benzylic H), 4.57 (d, J = 12 Hz, 1H, benzylic H), 4.42 (dd, J = 9 and 3 Hz, H-3), 3.99-3.95 (m, 2H, H-2, H-5), 3.90-3,80 (m, 2H, H-6), 1.06 (s, 9H, *t*-butyl).

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17. Reaction of methyl 4-*O*-azidoformyl-2,3,6-trideoxy-α-D-*threo*-hex-2-enopyranoside with iron (II) bromide afforded cyclic carbamate of methyl 3-amino-2-bromo-2,3,6-trideoxy-α-D-talopyranoside as a crystal and the single X-ray crystallography of this crystalline product confirmed the *syn* addition of amido group and bromine. ^{1}H-NMR spectral data also showed same coupling constants (to be published).