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Note

The application of the intermediate 2-methyl-glyco-[2,1-*d*]-2-oxazolines for glycoside synthesis☆

Sergey S. Pertel *, Vasily Ya. Chirva, Andrey L. Kadun, Elena S. Kakayan

Department of Organic Chemistry, National Taurida University, Yaltinskaya 4, Simferopol, Crimea 95007, Ukraine

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Abstract

The synthesis of 2-acylamino-2-deoxysugars 1,2-*trans*-glycosides is described via the oxazolinium salt generated from an O,N-acetylated 1,2-*cis*-glycosyl halide of 2-amino-2-deoxysugar under the conditions of halide-anion catalysis. This salt was then interacted with alcohol to form the corresponding 1,2-*trans*-glycoside. A method for removing the generated hydrogen chloride is described. The conditions of this synthesis allow glycosides with acid-labile functional groups to be obtained. Suppression of the anomerisation of 1,2-*trans*-glycosides was achieved by the introduction of *N*,*N*′-dicyclohexyl urea into the reaction medium.

Keywords: Glycosyl halides; Halide-ion catalysis; 1,2-*Trans*-glycosides of 2-acylamino-2-deoxysugars; Glyco-[2,1-*d*]-2-oxazolines; 1,2-*Trans*-glycosaminides anomerisation

The 2-substituted glyco-[2,1-*d*]-2-oxazolines are widely used in the synthesis of N-acetylated 1,2-*trans*-glycosaminides [1,2]. Fixation of the anomeric centre configuration during bicyclic system formation is an important advantage of the oxazoline method, providing glycosylation stereospecificity [3]. The sugars' oxazoline derivatives are comparatively unstable. Like other imidoesters, they are easily hydrolysed at the C=N bond when traces of protic acids are present [4]. Glycooxazolines are also easily subjected to elimination to form 2-acylaminoglycals [5,6]. As a rule, oxazoline stability decreases with the increase of their glycosylating activity. Therefore the glycoside synthesis method, with oxazolines being generated from a stable precursor directly in the reaction medium, would be an advantage.

2-Methylglycooxazolines can be easily obtained from *N*-acylglycosyl halides of 2-amino-2-deoxysugars by the Lemieux method [7]. In the conditions of halide-ion catalysis, the relatively stable 1,2-*cis*-glycosyl halides which are obtained are transformed into the reactive 1,2-*trans*-glycosyl halides. Treatment of these *trans*-halides by weak bases, sodium hydrogen carbonate for example, induces an amidic carbonyl intramolecular nucleophilic attack on the anomeric centre. As a result, the corresponding oxazoline derivatives are

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* Corresponding author. Fax: +380-652-232310.

E-mail address: orgchem@ccssu.crimea.ua (S.S. Pertel).

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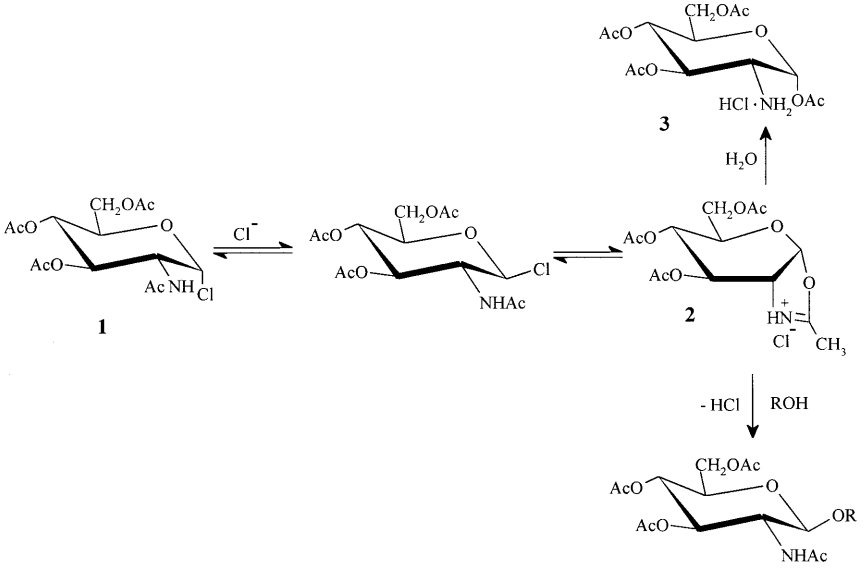
formed. The glycosylation of alcohols by sugar oxazoline derivatives is catalysed by protic acids [8,9] and Lewis acids [10–12]. The synthesis of glycooxazolines by the Lemieux method provides a base presence in the reaction medium, and therefore can not be combined with the glycoside synthesis.

We have found that oxazoline cycle formation also occurs in the absence of a base due to 1,2-*trans*-glycosyl halide spontaneous rearrangement (see Scheme 1). As a result, the equilibrium mixture contains the initial glycosyl halide and glyco-[2,1-*d*]-2-oxazoline hydrochloride when examined by TLC. The 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride **1** interaction with water in the presence of 0.5 equivalents of benzyltriethylammonium chloride in nitromethane led to the stereospecific formation of 2-amino-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose hydrochloride **3**, which crystallised from the solution with 90% yield (see Section 1). It was evident that this transformation could be an effective means of 2-acylamino-2-deoxysugar derivatives selective N-deacylation in mild conditions.

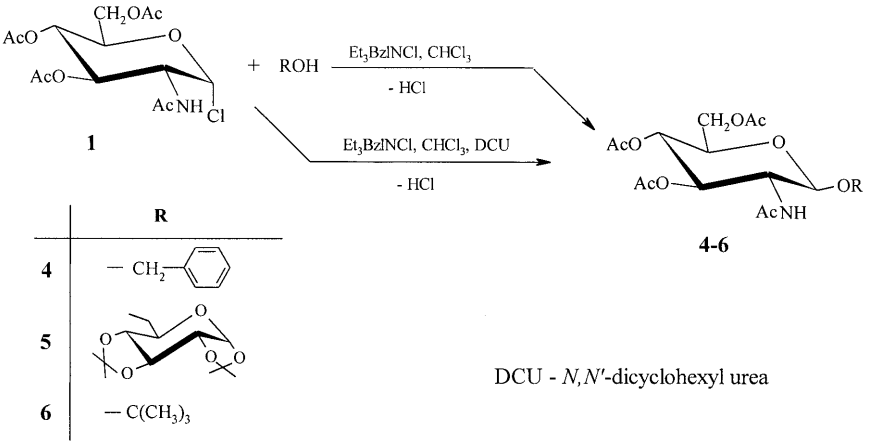
The oxazolinium salt **2**, an active glycosylating agent, gives the corresponding 1,2-*trans*-glycoside when alcohol is added instead of water. In this case, hydrogen halide is also a product that was removed from the reaction mixture to avoid destruction of the forming glycosides by refluxing of the reagent solution. The bases usually used for this are unsuitable as they deprotonate the oxazolinium ion and therefore decrease glycosylating agent concentration.

Thus the 1,2-*trans*-glycosaminide synthesis was realised by refluxing the solution containing the *N*-acylglycosyl halide, halide-anion with the corresponding alcohol. As high temperatures and polar solvents promote rearrangement of the oxazolines into 2-acylaminoglycals [5,6], the most suitable solvent was of low polarity with a boiling point less than 80 °C in which HCl hardly dissolves, e.g., chloroform, methylene chloride, 1,2-dichloroethane, benzene, carbon tetrachloride. A quaternary ammonium salt, e.g., triethylbenzylammonium chloride, was used as a halide anion source readily soluble in these media. It should be noted that the alternatives hydrogen bromide and hydrogen iodide cause a greater destruction of carbohydrate derivatives than hydrogen chloride and are readily soluble in the solvents used (Scheme 2).

The synthesis of compounds **4**–**6** demonstrated the described method for obtaining 1,2-*trans*-glycosides of N-acetylated 2-amino-2-deoxysugars. Benzylglycoside **4** and disaccharide **5** were obtained by interaction of glycosyl chloride **1** with 1.0–1.2 equivalents of the corresponding alcohol in the presence of



Scheme 1.



Scheme 2.

0.5 equivalents of triethylbenzylammonium chloride. The reaction proceeded over 15–18 h with refluxing of the reagent chloroform solution. Products **4** and **5** were obtained in 77 and 71% yields, respectively. For the *tert*-butyl glycoside **6**, a fourfold surplus of *tert*-butanol and 0.2 equivalents of triethylbenzylammonium chloride were used. Refluxing in chloroform solution for 24 h afforded the desired glycoside **6** in 55% yield.

The use of a large catalyst concentration in the glycosylation of alcohols with low reactivity promoted the formation of a significant amount of glycal, even at low (< 80 °C) temperatures. At high temperatures, this secondary reaction became predominant. When the boiling point of the being glycosylated alcohols was lower than that of the chosen solvent, it was necessary to use an excess of being glycosylated substance or multiple additional introductions into the reaction mixture.

Analysis of the reaction medium showed that in some cases, e.g., in the synthesis of *tert*-butyl glycoside **6**, the corresponding anomeric glycoside is present. As the oxazoline synthesis is highly stereospecific, we supposed that the 1,2-*cis*-glycoside is generated because of the previously formed 1,2-*trans*-glycoside anomerisation. The anomerisation catalysis was provided by traces of the protic acid being present in the reaction medium.

Hydrogen bromide is a stronger acid than hydrogen chloride, and the yield of the 1,2-*cis*-glycoside increased when bromide ion was used as a glycosylation catalyst. To prevent this undesirable anomerisation it was necessary to bind the remaining hydrogen halide with substituted ureas which are weak enough not to deprotonate the oxazolinium ion.

N,*N*′-Dicyclohexyl urea (DCU) was the most effective agent and not the widely used tetramethyl urea. *N*,*N*′-Dicyclohexyl urea (0.2–0.5 equivalents) suppressed the anomerisation completely in the reaction medium and promoted an increase in the yield of desired glycoside. For example, the yield of *tert*-butyl glycoside **6** increased from 55 to 68%, and the yield of benzyl glycoside **4** increased from 77 to 82% (see Section 1). The formation of anomeric 1,2-*cis*-glycosides was not observed using this glycosylation procedure, even with bromide as a catalyst. In most cases, *N*,*N*′-dicyclohexyl urea crystallised from the reaction medium after the solution was cooled. It was necessary to carefully control complete glycoside separation from the *N*,*N*′-dicyclohexyl urea. Glycosylation in the presence of *N*,*N*′-dicyclohexyl urea was optimum as anomerisation of 1,2-*trans*-glycoside was eliminated.

1. Experimental

General methods.—^{1}H NMR spectra were recorded at 200 MHz with a Bruker WP-200 spectrometer in $CDCl_3$. Chemical shifts are expressed in ppm downfield from Me_4Si. Thin-layer chromatography was performed on Silufol UV-254 plates — aluminium plates precoated with silica gel Silpearl UV-254 (Kavalier, Czech Republic). Detection was ac-

complished by heating to 300 °C. Column chromatography was performed with silica gel L-40/100 (Lachema, Czech Republic) using gradient elution from $CHCl_3$ to $CHCl_3$–EtOH (A) 100:0.5 (v/v), (B) 100:1 (v/v). Optical rotation was measured with a Polamat-S polarimeter. Melting points were determined in capillaries and were uncorrected.

1,3,4,6-Tetra-O-*acetyl-2-amino-2-deoxy*-α-D-*glucopyranose hydrochloride* (**3**).—2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride **1** (200 mg, 0.55 mmol) and triethylbenzylammonium chloride (25 mg, 0.2 equiv) were dissolved in nitromethane (2 mL) and water (20 μL, 2 equiv) was added to the solution. After 5 h, when TLC (10:1 (v/v) $CHCl_3$–EtOH) showed that the reaction was complete, the precipitate of the hydrochloride **3** was filtered. The filtrate and washings were then combined and evaporated. Nitromethane (2 mL) was added to the dry residue. After filtration of this mixture, an additional quantity of compound **3** was obtained. The total yield of **3** was 188 mg (90%): mp 186 °C, lit. 185 °C [13]; $[\alpha]^{21}_{546}$ +171° (*c* 2.0, water), lit. $[\alpha]^{20}_{D}$ +140° [13]; ^{1}H NMR (Me_2SO-d_6): δ 8.75 (bs, 3 H, NH_3^+), 6.20 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 5.25 (t, 1 H, $J_{3,4}$ 10 Hz, H-3)[1], 5.00 (t, 1 H, $J_{4,5}$ 10 Hz, H-4)[1], 4.18 (dd, 1 H, $J_{6a,6b}$12 Hz, H-6a), 4.13 (ddd, 1 H, $J_{5,6a}$ 3.6 Hz, H-5), 3.97 (dd, 1 H, $J_{6a,5}$ 2 Hz, H-6b), 3.86 (dd, 1 H, $J_{2,3}$ 10 Hz, H-2), 2.18, 2.03, 1.99 and 1.97 (4 s, 12 H, 4 Ac).

Benzyl-2-acetamido-3,4,6-tri-O-*acetyl-2-deoxy*-β-D-*glucopyranoside* (**4**)

Method (a). 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride **1** (200 mg, 0.55 mmol) and triethylbenzylammonium chloride (62 mg, 0.5 equiv) were dissolved in abs $CHCl_3$ (6 mL). Then 3 mL of $CHCl_3$ was evaporated to remove trace water. Absolute benzyl alcohol (71 μL, 1.2 equiv) was added to the cooled solution and the mixture was boiled under reflux for 15 h. The reaction was monitored by TLC with 10:0.5 (v/v) $CHCl_3$–EtOH. After completion ($\approx$15 h), the solvent was evaporated. The dry residue was chromatographed on a column of silica gel using $CHCl_3 \rightarrow$ mixture A, followed by crystallisation from a $CHCl_3$–Et_2O mixture to give **4** (186 mg, 77%): mp 164–165 °C, lit. 165 °C [14]; $[\alpha]^{30}_{546}$ −59° (*c* 1.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 7.38–7.22 (m, 5 H, Ar-H), 5.40 (d, 1 H, $J_{NH,2}$ 8 Hz, NH), 5.21 (dd, 1 H, $J_{3,4}$ 9.3 Hz, H-3), 5.09 (dd, 1 H, $J_{4,5}$ 9.3 Hz, H-4), 4.9 (d, 1 H, $J_{PhCHa,PhCHb}$ 12 Hz, PhCHa), 4.63 (d, 1 H, $J_{1,2}$ 8.1 Hz, H-1), 4.6 (d, 1 H, PhCHb), 4.37 (dd, 1 H, $J_{6a,6b}$ 12 Hz, H-6a), 4.13 (dd, 1 H, $J_{6b,5}$ 2.4 Hz, H-6b), 3.95 (ddd, 1 H, $J_{2,3}$ 9.6 Hz, H-2), 3.66 (ddd, 1 H, $J_{5,6a}$ 4.5 Hz, H-5), 2.11, 2.02, 2.015 and 1.91 (4 s, 12 H, 4 Ac).

Method (b). The synthesis of benzyl-2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside was carried out as described in method (a). In addition, *N*,*N*′-dicyclohexyl urea (DCU, 24 mg, 0.2 equiv) was introduced in the reaction medium. After reaction completion and cooling of the solution, the DCU was removed by filtration. Purification on a column of silica gel followed by crystallisation according to method (a) gave 197 mg (82%) of the title compound.

6-O-*(2-Acetamido-3,4,6-tri*-O-*acetyl-2-deoxy*-β-D-*glucopyranosyl)-1,2:3,4-di*-O-*isopropylidene*-α-D-*galactopyranose* (**5**).—2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride **1** (210 mg, 0.57 mmol), 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (150 mg, 1 equiv), and triethylbenzylammonium chloride (65 mg, 0.5 equiv) were dissolved in abs $CHCl_3$ (8 mL) and the solution was half evaporated. The mixture was then boiled under reflux for 18 h with reaction process monitoring by TLC using a 10:0.5 (v/v) mixture of $CHCl_3$–EtOH. After completion, the solvent was removed and the product was chromatographed on a column of silica gel using $CHCl_3 \rightarrow$ mixture B, followed by crystallisation from a $CHCl_3$–Et_2O mixture, to give **5** (240 mg, 71%): mp 100–101 °C, lit. 99–102 °C [15]; $[\alpha]^{30}_{546}$ −71° (*c* 1.4, CH_2Cl_2), lit. $[\alpha]_D$ −66° [15]; ^{1}H NMR ($CDCl_3$): δ 5.53 (d, 1 H, $J_{NH,2'}$ 9 Hz, NH), 5.47 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.06 (m, 2 H, H-3′ + H-4′), 4.64 (d, 1 H, $J_{1',2'}$ 9 Hz, H-1′), 4.51 (dd, 1 H, $J_{3,2}$ 2 Hz, H_3), 4.25 (dd, H-2), 4.20 (dd, $J_{6a',5'}$ 4.5, $J_{6a',6b'}$ 13 Hz, H-6a′), 4.07 (dd, $J_{4,5}$ 1.8 Hz, $J_{4,3}$ 8 Hz, H-4), 4.06 (dd, $J_{6b',5'}$ 2.4 Hz, H-6b′), 3.93 (m, 2 H, H-2′ + H-5′), 3.91 (dd, 1 H, $J_{6a,6b}$ 12.4 Hz, $J_{6a,5}$ 2.4 Hz, H-6a), 3.67 (dd, 1 H, $J_{6b,5}$ 8.8 Hz, H-6b), 3.62 (ddd, 1 H, H-5),

[1] The assignment can be inverse.

2.02, 1.96, 1.95 and 1.90 (4 s, 12 H, 4 Ac), 1.44, 1.38 and 1.25 (3 s, 12 H, 2 Me_2C).

Tert-*butyl-2-acetamido-3,4,6-tri*-O-*acetyl-2-deoxy-β*-D-*glucopyranoside* (**6**)

Method (a). 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride **1** (200 mg, 0.55 mmol) and triethylbenzylammonium chloride (25 mg, 0.2 equiv) were dissolved in abs $CHCl_3$ (6 mL) and the solution was half evaporated. *Tert*-butanol (102 μL, 2 equiv) was added to the solution, and the mixture was boiled under reflux for 12 h. More *tert*-butanol (102 μL) was then added to the reaction mixture and the refluxing was continued for a further 12 h. The reaction was monitored by TLC using a 10:0.5 (v/v) mixture of $CHCl_3$–EtOH. The solution was evaporated to dryness. The dry residue was then chromatographed on a column of silica gel using $CHCl_3 \rightarrow$ mixture A, followed by crystallisation from a $CHCl_3$–Et_2O mixture, to afford **6** (122 mg, 55%): mp 169–171 °C; $[\alpha]_{546}^{30}$ −2° (*c* 1.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 5.52 (d, 1 H, $J_{NH,2}$ 8.4 Hz, NH), 5.39 (dd, 1 H, $J_{3,4}$ 9.2 Hz, H-3), 4.90 (dd, 1 H, $J_{4,5}$ 9.8 Hz, H-4), 4.88 (d, 1 H, $J_{1,2}$ 8.4 Hz, H-1), 4.17 (dd, 1 H, $J_{6a,6b}$ 12.2 Hz, H-6a), 4.00 (dd, 1 H, $J_{6b,5}$ 2.6 Hz, H-6b), 3.67 (ddd, 1 H, $J_{5,6a}$ 5.8 Hz, H-5), 3.51 (ddd, 1 H, $J_{2,3}$ 10.6 Hz, H-2), 1.99, 1.965, 1.96 and 1.86 (4 s, 12 H, 4 Ac), 1.16 (s, 9 H, $C(CH_3)_3$).

Method (b). The synthesis of the glycoside **6** was carried out as described in method (a). In addition, DCU (61 mg, 0.5 equiv) was introduced into the reaction medium. After completion of the reaction and cooling of the solution, the DCU was removed by filtration. The product was obtained as described above, to afford **6** (150 mg, 68%).

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References

[1] S.E. Zurabyan, A.Ya. Khorlin, *Russ. Chem. Rev.*, 43 (1974) 887–904.
[2] R. Kaifu, T. Osawa, *Carbohydr. Res.*, 52 (1976) 179–185.
[3] A.F. Bochkow, G.E. Zaikov, *Chemistry of the O-Glycosidic Bond: Formation and Cleavage*, Pergamon, Oxford, 1979, p. 48.
[4] S.S. Pertel, A.L. Kadun, V.Ya. Chirva, *Bioorgan. Khim.*, 21 (1995) 226–229.
[5] W.L. Salo, H.G. Fletcher, Jr., *J. Org. Chem.*, 34 (1969) 3189–3191.
[6] S. David, A. Veyrieres, *Carbohydr. Res.*, 40 (1975) 23–29.
[7] R.U. Lemieux, H. Driguez, *J. Am. Chem. Soc.*, 97 (1975) 4063–4069.
[8] R. Kaifu, T. Osawa, R.W. Jeanloz, *Carbohydr. Res.*, 40 (1975) 111–117.
[9] S. David, A. Veyrieres, *Carbohydr. Res.*, 40 (1975) 23–29.
[10] M.A. Nashed, M. Kiso, C.W. Slife, L. Anderson, *Carbohydr. Res.*, 90 (1981) 71–82.
[11] T. Ogawa, K. Beppu, S. Nakabayashi, *Carbohydr. Res.*, 93 (1981) C6–C9.
[12] J. Dahmen, G. Gnosspelius, A.-C. Larsson, T. Lave, G. Noori, K. Pålsson, *Carbohydr. Res.*, 138 (1985) 17–28.
[13] D. Horton, *Adv. Carbohydr. Chem.*, 15 (1960) 159–200.
[14] H.H. Zu, L.N. Congson, *Can. J. Chem.*, 70 (1992) 2607–2617.
[15] P. Rollin, P. Sinay, *J. Chem. Soc., Perkin Trans. 1*, (1977) 2513–2517.