A Novel Glycoside Anomerization Catalyzed by Trimethylsilyl Bromide and Zinc Bromide in Combination

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A novel glycoside anomerization occurred when trimethylsilyl bromide (TMSBr) and zinc bromide were utilized in combination as a catalyst. Treatment of β-glycosides with TMSBr and zinc bromide in the presence of alcohols afforded anomerized products in good yields.

Keywords glycoside anomerization; trimethylsilyl halide; zinc halide; glucosamine; Lewis acid

In our preceding paper,[1] we reported the stereoselective glycosidation of **4** and **2a—d** to afford β-anomers (**1a—d**) by the combined use of trityl chloride (TrCl) and zinc chloride as an activator. When a zinc halide was used alone as an activator, only the α-anomers (**3a—d**) were obtained. These results suggest that the presence of TrCl may inhibit the anomerization of β-anomers (**1a—d**), and so we investigated the mechanism of the anomerization. We now report a novel glycoside anomerization catalyzed by a combination of trimethylsilyl bromide (TMSBr) and zinc bromide.

It is well known that glycoside anomerization proceeds in the presence of Lewis acids such as $TiCl_4$, $AlCl_3$, $ZnCl_2$, $SnCl_2$, $BF_3 \cdot Et_2O$, *etc.*[2] When the β-anomer (**1a**) was treated with Lewis acids such as $AgClO_4$, $ZnCl_2$ or $ZnBr_2$ in the presence of **2a**, however, no reaction occurred and the starting material was recovered (see Table I, run 1). Since the anomerization was thought to take place in the reaction system for the glycosidation of **4** and **2a** using $AgClO_4$, $ZnCl_2$ or $ZnBr_2$, we became interested in the anomerization mechanism.

Hydrogen bromide (HBr) would probably be formed during the glycosidation of **4** and **2a**, and so we anticipated that the resulting proton acid would participate in the anomerization.[2] Attempted anomerization of the β-anomer (**1a**) with HBr, however, resulted in the recovery of the starting material. After investigation of the reaction conditions, the anomerization was proved to take place in the presence of both HBr and Lewis acid. Thus, when the β-anomer (**1a**) was treated with $ZnBr_2$ in the presence of HBr in dichloromethane for 3 h at room temperature, the α-anomer (**3a**) was obtained in 50% yield along with the bromide (**4**)[3] in 34% yield (Table I, run 2). It must be emphasized that the presence of both HBr and Lewis acid is necessary for the anomerization to proceed. These results suggest that an active species generated from HBr and $ZnBr_2$ acts as a catalyst on the anomerization.[4]

Since the combination of HBr and Lewis acid was found to act as a catalyst on the anomerization, we searched for milder reaction conditions. We anticipated that TMSBr and $ZnBr_2$ in combination should also act as a catalyst.[5] Treatment of **1a** with TMSBr (1.5 eq) and $ZnBr_2$ (1.5 eq) in dichloromethane at room temperature for 20 h afforded the anomerized product (**3a**) in 54% yield along with the 1-bromo sugar (**4**) (Table I, run 3). When the reaction was carried out in the presence of 1 eq of the alcohol (**2a**) for

TABLE I. Anomerization of **1a—e** Catalyzed by the Combined Use of Trimethylsilyl Halide and Zinc Halide

Run	Substrate	Catalyst	Alcohol (eq)	Time[a] (h)	Products (% yield[b])
1	**1a**	$ZnBr_2$	**2a** (1.0)	24	—[c]
2	**1a**	$ZnBr_2$–HBr	**2a** (0)	3	**3a** (50), **4** (34)
3	**1a**	$ZnBr_2$–TMSBr	**2a** (0)	20	**3a** (54), **4** (10)
4	**1a**	$ZnBr_2$–TMSBr	**2a** (1.0)	4	**3a** (97)
5	**1a**	$ZnCl_2$–TMSCl	**2a** (1.0)	48	**3a** (34), **5** (38)
6	**1a**	TMSBr	**2a** (1.0)	24	—[c]
7	**1b**	$ZnBr_2$–TMSBr	**2b** (1.0)	1	**3b** (88)
8	**1c**	$ZnBr_2$–TMSBr	**2c** (1.0)	1	**3c** (88)
9	**1d**	$ZnBr_2$–TMSBr	**2d** (1.0)	24	**3d** (75), **4** (6)
10	**1e**	$ZnBr_2$–TMSBr	**2e** (1.0)	24	**3e** (71), **4** (5)

a) All reactions were carried out in dichloromethane at room temperature. *b*) Isolated yield. *c*) No reaction occurred, and the starting material (**1a**) was recovered.

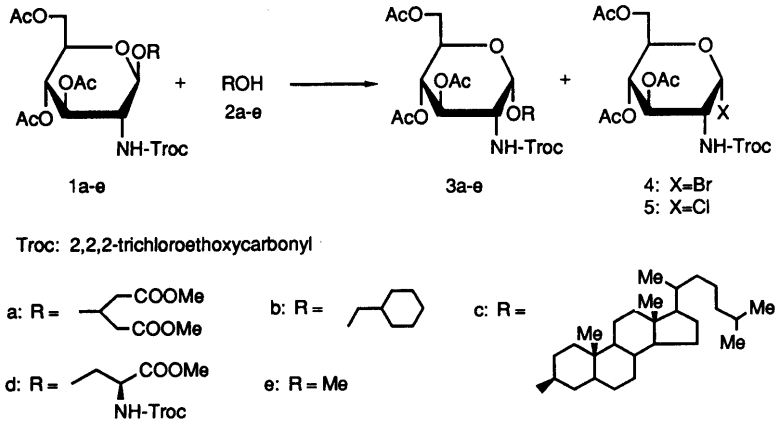

Chart 1

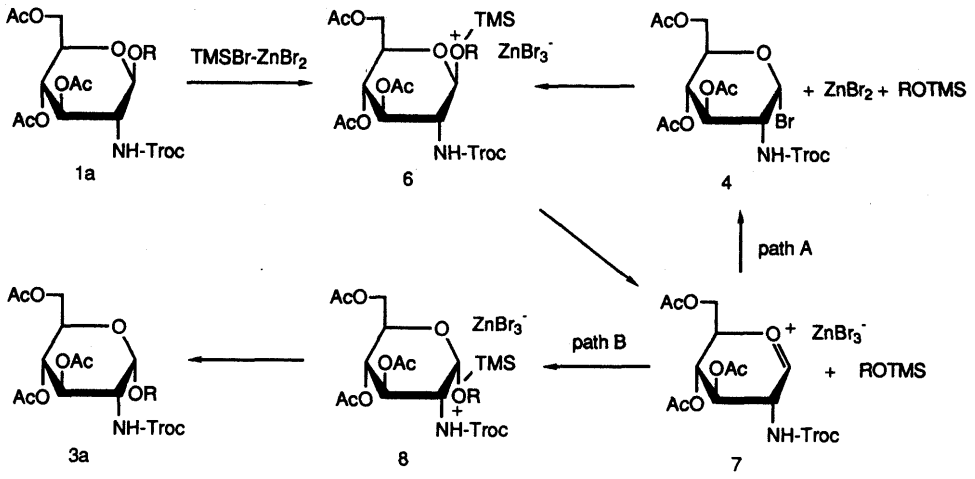

Chart 2

4 h at room temperature, **3a** was obtained in 97% yield (Table I, run 4). Anomerization of **1a** with a large excess of $ZnCl_2$ and trimethylsilyl chloride (TMSCl) afforded **3a** and the 1-chloro sugar (**5**) in 34% and 38% yields, respectively (Table I, run 5). No reaction occurred when **1a** was treated with TMSBr alone (Table I, run 6).[6] Attempted anomerization of the α-anomer (**3a**) to the β-anomer (**1a**) by the combined use of TMSBr and $ZnBr_2$ resulted in the recovery of the starting material (**3a**).

A possible mechanism for the anomerization of **1a** to **3a** catalyzed by TMSBr and $ZnBr_2$ is shown in Chart 2. Thus, an oxonium salt (**6**), formed by the reaction of **1a** and the active species generated from TMSBr and $ZnBr_2$, collapses to **7** with liberation of the trimethylsilyl ether. Next, the reaction may proceed *via* two pathways. The bromide (**4**) was presumed to have been formed by bromination of the intermediate (**7**) with the resulting activated brominium anion (path A). Formation of the thermodynamically more stable anomerized compound (**3a**) would be accounted for by the conversion of **7** to an intermediate (**8**) by the attack of the ROTMS from the α side, followed by the liberation of TMSBr (path B). When the alcohol (**2a**) is present in the reaction system, path B is considered to be predominant from the above experimental results (Table I, run 4).

The success of the glycoside anomerization using TMSBr and $ZnBr_2$ prompted us to apply this methodology to other glycosides (**1b**—**e**).[1,7] The results are summarized in Table I. All the anomerization reactions of β-anomers (**1b**—**e**) with TMSBr and $ZnBr_2$ in the presence of alcohols (**2b**—**c**) afforded anomerized products (**3b**—**e**) in good yield (Table I, runs 7—10).

In summary, a novel anomerization occurred when the combination of TMSBr and $ZnBr_2$ was utilized as a catalyst. The reaction conditions were extremely mild, so this new method should be widely applicable in carbohydrate chemistry.

Experimental

Melting points were determined on a Yanagimoto melting point apparatus, and are uncorrected. Infrared (IR) spectra were taken on a Hitachi 270-30 infrared spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained in deuteriochloroform on a JEOL GSX 500 spectrometer (500 MHz). Chemical shifts are reported in parts per million relative to tetramethylsilane (δ units) as an internal standard. Optical rotations were measured with a Horiba SEDA 200 polarimeter. Column chromatography was performed with Merck Silica gel 60 (70—230 mesh).

Anomerization of 1a with Combined Use of HBr and Zinc Bromide A mixture of **1a** (40 mg, 0.063 mmol), $ZnBr_2$ (14 mg, 0.063 mmol) and 0.17 N HBr–dichloromethane (1 ml) was stirred for 3 h at room temperature. The reaction mixture was diluted with AcOEt and washed with 5% $NaHCO_3$ and water, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel (10 g) using chloroform–acetone (50 : 1) to give 12 mg (34%) of the bromide (**4**) and 20 mg (50%) of **3a**, as oils, in order of elution. The NMR spectra of **4** and **3a** were identical with those of authentic samples.[1]

Anomerization of 1a with Combined Use of TMSBr and Zinc Bromide A mixture of **1a** (85 mg, 0.13 mmol), TMSBr (30 mg, 0.20 mmol) and $ZnBr_2$ (44 mg, 0.20 mmol) in dichloromethane (2 ml) was stirred for 20 h at room temperature. The reaction mixture was diluted with AcOEt, washed with 5% $NaHCO_3$ and water, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel (20 g) using chloroform–acetone (50 : 1) to give 46 mg (54%) of **3a**, as a colorless oil.

Anomerization of 1a with Combined Use of TMSCl and Zinc Chloride A mixture of **1a** (125 mg, 0.20 mmol), the alcohol **2a** (35 mg, 0.20 mmol), TMSCl (1 ml, 6.50 mmol) and zinc chloride (300 mg, 2.20 mmol) in dichloromethane (2 ml) was stirred for 24 h at room temperature. The reaction mixture was diluted with AcOEt, washed with 5% $NaHCO_3$ and water, dried over $MaSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel (20 g) using chloroform–acetone (50 : 1) to give 37 mg (38%) of **5** and 42 mg (34%) of **3a**, as colorless oils, in order of elution.

5: ^{1}H-NMR δ: 2.05 (3H, s, $OCOCH_3$), 2.08 (3H, s, $OCOCH_3$), 2.11 (3H, s, $OCOCH_3$), 4.13 (2H, m, H-5, H-2), 4.27 (1H, m, H-2), 4.33 (1H, dd, J=13.0, 4.0 Hz, H-6), 4.66 (1H, d, J=11.9 Hz, $COOCH_2CCl_3$), 4.81 (1H, d, J=11.9 Hz, $COOCH_2CCl_3$), 5.24 (1H, t, J=9.0 Hz, H-4), 5.37 (1H, m, H-3), 6.53 (1H, d, J=4.0 Hz, H-1), 6.80 (1H, br, NH).

Typical Procedure for Anomerization with Combined Use of TMSBr and Zinc Bromide in the Presence of the Alcohol A mixture of **1a** (125 mg, 0.20 mmol), the alcohol **2a** (27 mg, 0.15 mmol), TMSBr (46 mg, 0.31 mmol) and zinc bromide (75 mg, 0.31 mmol) in dichloromethane (2 ml) was stirred for 4 h at room temperature. The reaction mixture was diluted with AcOEt, washed with 5% $NaHCO_3$ and water, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel (20 g) using chloroform–acetone (50 : 1) to give 121 mg (97%) of **3a**, as a colorless oil.

Compound **3e** was prepared from **1e**[7] according to the typical procedure described above. **3a**: mp 119—124 °C. $[\alpha]_D^{25}$ +64.7° (c=1.45, $CHCl_3$). *Anal.* Calcd for $C_{16}H_{22}Cl_3NO_{10}$: C, 38.85; H, 4.48; N, 2.83. Found: C, 38.90; H, 4.59; N, 2.97. IR (KBr): 3376, 1755, 1554, 1452, 1374, 1230, 1170 cm^{-1}. ^{1}H-NMR δ: 2.00, 2.03, 2.10 (each 3H, s, $OCOCH_3$), 3.43 (3H, s, OCH_3), 3.96 (1H, ddd, J=10.0, 4.0, 2.0 Hz, H-5), 4.06 (1H, dd, J=10.0, 3.0 Hz, H-2), 4.11 (1H, dd, J=12.0, 2.0 Hz, H-6), 4.26 (1H, dd, J=12.0, 4.0 Hz, H-6), 4.63 (1H, d, J=11.9 Hz, $COOCH_2CCl_3$), 4.78 (1H, d, J=3.0 Hz, H-1), 4.81 (1H, d, J=11.9 Hz, $COOCH_2CCl_3$), 5.11 (1H, t, J=10.0 Hz, H-4), 5.26 (1H, t, J=10.0 Hz, H-3), 5.26 (1H, d, J=10.0 Hz, NH).

References and Notes

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4) In the case of glycosidation of **4** and **2a—d** by the combined use of TrCl and zinc chloride, it was presumed that the generation of an active species from HBr and zinc chloride was inhibited by the presence of TrCl and hence on anomerization occurred, giving the β-anomers (**1a—d**) with high stereoselectivity.
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7) K. Higashi, K. Nakayama, E. Shioya, and T. Kusama, unpublished work. Compound **1e** was prepared in two steps from 2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-D-glucose. The details of the synthesis of **1e** will be reported at a later date.