# Novel Degradation of Sugar Skeleton by Diazidation

**Masataka Yokoyama,* Naoki Kobayashi, Takeshi Hachiya, Misao Kubo, and Hideo Togo**

Department of Chemistry, Faculty of Science, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263

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*O*-Benzylated acyclic sugars are allowed to react with azidotrimethylsilane in the presence of boron trifluoride–diethyl ether to afford the corresponding 1,1-diazido sugars, cyano sugars, and interestingly, 1,1-diazido sugars degradated at the 1-position of carbon.

Thermolysis and photolysis of D-glucopyranosylidene diazide have not generated the corresponding carbene, but rather the corresponding azidonitrene; this results in the formation of sugar tetrazoles.[1] As an extension of this reaction, we have been interested in the reactions of 1,1-diazido acyclic sugars. In the examination of the diazidation of the starting compounds, we found a novel degradation of the sugar skeleton. Here this reaction is reported and its tentative mechanism is described.

## Results and Discussion

Previously, the yields of 1,1-diazido acyclic sugars have been reported to be very low (1,1-diazido-2,3,4,5,6-penta-*O*-benzyl-1,1-dideoxy-D-glucose hydrate (**2a**)=8%; 1,1-diazido-2,3,4,5-tetra-*O*-benzyl-1,1-dideoxy-D-arabinose hydrate (**2b**)=30%; 1,1-diazido-2,3,4-tri-*O*-benzyl-1,1-dideoxy-D-erythrose hydrate (**2c**)=29%; 1,1-diazido-2,3-di-*O*-benzyl-1,1-dideoxyglyceraldehyde hydrate (**2d**)=21%; 1,1-diazido-2,3,4,5-tetra-*O*-benzyl-1,1-dideoxy-D-ribose hydrate (**2e**)=19%).[1] The diazidation reaction was reinvestigated in further detail in hopes of increasing the yields of these starting compounds. It was found that the expected 1,1-diazido acyclic sugars, the corresponding cyano sugars, and surprisingly, an one-carbon degradated 1,1-diazido acyclic sugar were obtained by diazidation with $TMSN_3$ and $BF_3{\cdot}OEt_2$.

Some known diazidation reactions were tried by using such reagents as $NaN_3/ZnCl_2$ or $SnCl_2$,[2a] $NaN_3/TiCl_4$,[3] and $NaN_3$/15-crown-5.[2b] However, the expected 1,1-diazido acyclic sugars could not be obtained satisfactorily. Therefore, the reaction reagents available to obtain the expected compound were limited to $TMSN_3/BF_3{\cdot}OEt_2$.

In order to get the optimum yield of this reaction, a control experiment was carried out by changing the amount of $BF_3{\cdot}OEt_2$, reaction temperature, and time in the reaction of 2,3,4,5,6-penta-*O*-benzyl-D-glucose (**1a**). The result is summarized in Table 1. Entry 3 showed the best conditions (2 mol amt. $BF_3{\cdot}OEt_2$, 0 °C, 3 h) to give **2a** in 47% yield together with 27% of 2,3,4,5,6-penta-*O*-benzyl-D-glucononitrile (**3a**). The formation of **2b** was observed in Entries 1, 4, and 6. The result shows that high temperature accelerates the degradation of the sugar skeleton. The same tendency was also revealed in the following control experiment for 2,3,4-tri-*O*-benzyl-D-erythrose (**1c**) (Table 2): High yield of **2c** was observed in Entry 4 and the degradation of sugar skeleton also took place at room temperature.

Table 1. The result of control experiments using **1a** in which the amount of $BF_3{\cdot}OEt_2$, reaction temperature, and time were changed. **1a**⟶**2a**+**2b**+**3a**

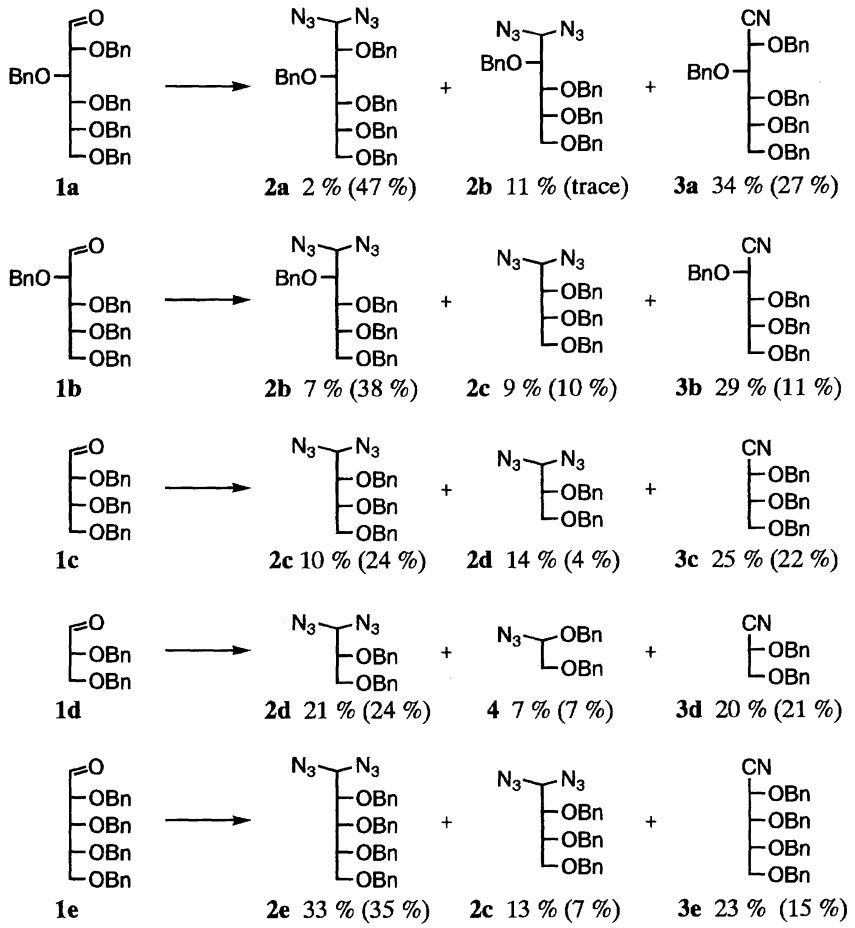
| Entry | Conditions | | | Yields (%) | | |
|---|---|---|---|---|---|---|
| | $BF_3{\cdot}OEt_2$/mol amt. | Temp/°C | Time/h | **2a** | **2b** | **3a** |
| 1 | 2 | R.T. | 6 | 2 | 11 | 34 |
| 2 | 2 | 0 | 6 | 32 | 0 | 28 |
| 3 | 2 | 0 | 3 | 47 | 0 | 27 |
| 4 | 2 | R.T. | 3 | 38 | 5 | 23 |
| 5 | 4 | 0 | 3 | 36 | 0 | 22 |
| 6 | 1 | R.T. | 6 | 10 | 14 | 24 |

Similarly, 2,3,4,5-tetra-*O*-benszyl-D-arabinose (**1b**), 2,3-di-*O*-benzyl-glyceraldehyde (**1d**), and 2,3,4,5-tetra-*O*-benzyl-D-ribose (**1e**) were treated under such conditions as 2 mol amt. $BF_3{\cdot}OEt_2$, r.t., 3 h to give **2b** (7%), **2c** (9%), **3b** (29%), **2d** (20%), **4** (7%), **3d** (20%) and **2e** (33%), **2c** (13%), **3e** (23%), respectively. The result is summarized in Scheme 1.

In the present reaction, the degradation of C-1 in the acyclic sugar was verified by the following facts: (1) By the diazidation of acyclic sugars, **1a** was changed to **2b**, **1b** to **2c**, and **1c** to **2d**; (2) The diazidation of mannose was found to afford **2b**, a product degradated from **1a**, in 33% yield; (3) The starting glucose labeled with $^{13}C$ at 1-position of **1a** afforded a non-labeled **2b**. These results suggest, the degradation

Table 2. The same as Table 1. Starting compound is **1c**. **1c**⟶**2c**+**2d**+**3c**

| Entry | Conditions | | | Yields (%) | | |
|---|---|---|---|---|---|---|
| | $BF_3{\cdot}OEt_2$/mol amt. | Temp/°C | Time/h | **2c** | **2d** | **3c** |
| 1 | 2 | R.T. | 6 | 10 | 14 | 25 |
| 2 | 1 | R.T. | 6 | 29 | Trace | 30 |
| 3 | 4 | R.T. | 6 | 3 | 6 | 34 |
| 4 | 2 | 0 | 6 | 35 | 0 | 22 |
| 5 | 3 | R.T. | 3 | 14 | 4 | 28 |




**Transfer conditions: $TMSN_3$ / $BF_3{\cdot}OEt_2$, r.t.;**
**the value of parenthesis shows the yeild under $TMSN_3$ / $BF_3{\cdot}OEt_2$, 0 °C.**

Scheme 1. Diazidation of *O*-benzylated acyclic sugars (D-glucose deriv.=**1a**, D-arabinose deriv.=**1b**, D-erythrose deriv.=**1c**, glyceraldehyde deriv.=**1d**, D-ribose deriv.=**1e**). These are treated with $TMSN_3$, $BF_3{\cdot}OEt_2$ (2 mol amt.) at r.t., 3 h, and under 0 °C.

mechanism shown in Scheme 2: **1a** reacts with $TMSN_3$ to give the corresponding addition product **5**, which reacts with another $TMSN_3$ to afford **2a** via path a. The evolution of nitrogen gas from **6** gives **3a** via path b. On the other hand, the formation of **2b** from **5** takes place perhaps via an intermediate **7**. The degradation mechanism of **5** to **7** (path c) can not be elucidated by the present experiment. The presence of the intermediate **5** is estimated by isolation of the compound (MS : *m/z* 784; IR: 2100 $cm^{-1}$; NMR shows the peak of TMS).

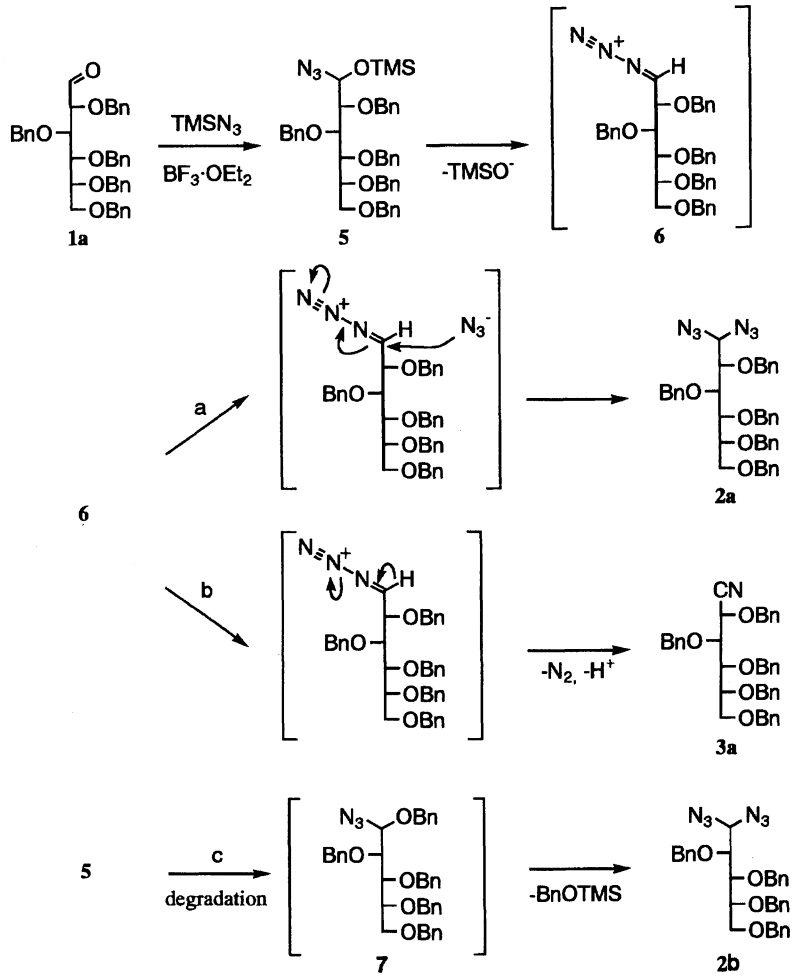
In conclusion 1,1-diazido sugars can be obtained, even though with low yield, using $BF_3{\cdot}OEt_2$ under 0 °C (Scheme 1). Further, the 1,1-diazido derivatives of unavailable D-erythrose and D-threose can easily be obtained from the respective D-ribose and D-xylose[4] by using the present method at room temperature.

## Experimental

Microanalyses were performed with Perkin–Elmer 240B and 2400 elemental analysers at the Chemical Analysis Center of Chiba University.

IR and $^1H$ NMR were measured with Hitachi-215, JEOL-JNM-FX270, JEOL-GSX-400, and JEOL-GSX-500 spectrometers. $^{13}C$ NMR was measured with a JEOL-JNM-FX270 spectrometer. Mass spectra (FAB) were measured using 3-nitrobenzyl alcohol (NBA) matrix on JEOL-HX110 spectrometer (KI or NaCl was added when $M^+$ didn't appear). Wakogel C-200 was used for column chromatography, Kieselgel 60 F254 (Merck) for TLC, and Wakogel B-5F for preparative TLC (PTLC). Columns JAIGEL-GS 320 (methanol) and J-53-4F13 (chloroform) were used for a recycling preparative HPLC (Japan Analytical Industry Co. HPLC-908).

**General Method of Diazidation.** Diazidation of 2,3,4,5,6-penta-*O*-benzyl-D-glucose (**1a**): To a solution of **1a** (1.00 g, 1.59 mmol) in dichloromethane (10 ml) under argon was added dropwise azidotrimethylsilane (0.84 ml, 6.34 mmol) and boron trifluoride–diethyl ether (0.36 ml, 3.18 mmol). The resulting mixture was stirred for 3 h at 0 °C, and then was quenched with aq sodium hydrogencarbonate, and extracted with chloroform (3×20 ml). The combined extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by both PTLC (hexane–ethyl acetate=4 : 1) and recycling preparative HPLC with chloroform to give **2a** and **3a** in




Scheme 2. Possible reaction pathway for the formation of diazido sugar **2a**, cyano sugar **3a**, and C-1 degradated diazido sugar **2b**.

47 and 27% yields, respectively.

The diazidation of **1b**, **1c**, **1d**, **1e**, and 2,3,4,5,6-penta-*O*-benzyl-D-mannose were carried out by the method mentioned above.

The structures of **2a**, **2b**, **2c**, **2d**, and **2e** were determined by our authentic samples.[1b)]

**Label Experiment.** D-Glucose-1-$^{13}$C was changed to 2,3,4,5,6-penta-*O*-benzyl-D-glucose-1-$^{13}$C via dithioketal formation,[5)] benzylation, and dithioketal cleavage.[6)]

**2,3,4,5,6-Penta-*O*-benzyl-D-glucononitrile (3a):** Colorless oil; IR (neat) 3050, 3020, 2920, 2860, 2280 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 3.62 (dd, 1H, $J$ = 3.90, 10.26 Hz, 6-Ha), 3.79 (ddd, 1H, $J$ = 3.42, 3.90, 6.35 Hz, 5-H), 3.83 (dd, 1H, $J$ = 3.42, 10.26 Hz, 6-Hb), 4.01 (dd, 1H, $J$ = 3.90, 6.35 Hz, 3-H), 4.11 (dd, 1H, $J$ = 3.90, 6.35 Hz, 4-H), 4.57 (d, 1H, $J$ = 6.35 Hz, 2-H), 4.36—4.85 (m, 10H, Ph-$CH_2$), 7.16—7.33 (m, 25H, Ph). HRMS. (FAB) Found: *m/z* 628.3063. Calcd for $C_{41}H_{42}NO_5$: M+H$^+$, 628.3063.

**2,3,4,5-Tetra-*O*-benzyl-D-arabinononitrile (3b):** Colorless oil; IR (neat) 3000, 2850, 2280 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 3.62 (dd, 1H, $J$ = 3.66, 10.44 Hz, 5-Ha), 3.74 (dd, 1H, $J$ = 3.30, 10.44 Hz, 5-Hb), 3.80 (ddd, 1H, $J$ = 3.30, 3.66, 7.70 Hz, 4-H), 4.02 (dd, 1H, $J$ = 3.11, 7.70 Hz, 3-H), 4.57 (d, 1H, $J$ = 3.11 Hz, 2-H), 4.29—4.92 (m, 8H, Ph-$CH_2$), 7.13—7.33 (m, 20H, Ph). HRMS. (FAB) Found: *m/z* 508.2487. Calcd for $C_{33}H_{34}NO_4$: M+H$^+$, 508.2486.

**2,3,4-Tri-*O*-benzyl-D-erythrononitrile (3c):** Colorless oil; IR (neat) 3030, 2850, 2280 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 3.59 (dd, 1H, $J$ = 4.40, 10.26 Hz, 4-Ha), 3.63 (dd, 1H, $J$ = 4.76, 10.26 Hz, 4-Hb), 3.87 (ddd, 1H, $J$ = 4.40, 4.76, 6.23 Hz, 3-H), 4.47 (d, 1H, $J$ = 6.23 Hz, 2-H), 4.45—4.87 (m, 6H, Ph-$CH_2$), 7.23—7.36 (m, 15H, Ph). HRMS. (FAB) Found: *m/z* 388.1885. Calcd for $C_{25}H_{26}NO_3$: M+H$^+$, 388.1911.

**2,3-Di-*O*-benzyl-glyceronitrile (3d):** Colorless oil; IR (neat) 3030, 2850, 2280 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ = 3.75 (dd, 1H, $J$ = 5.78, 10.45 Hz, 3-Ha), 3.77 (dd, 1H, $J$ = 5.50, 10.45 Hz, 3-Hb), 4.33 (ddd, 1H, $J$ = 5.50, 5.78 Hz, 2-H), 4.57—4.89 (m, 4H, Ph-$CH_2$), 7.25—7.39 (m, 10H, Ph). HRMS. (FAB) Found: *m/z* 268.1324. Calcd for $C_{17}H_{18}NO_2$: M+H$^+$, 268.1338.

**2,3,4,5-Tetra-*O*-benzyl-D-ribononitrile (3e):** Colorless oil; IR (neat) 3000, 2850, 2280 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 3.58 (dd, 1H, $J$ = 4.03, 10.62 Hz, 5-Ha), 3.66 (dd, 1H, $J$ = 3.67, 10.62 Hz, 5-Hb), 3.74 (ddd, 1H, $J$ = 3.67, 4.03, 6.96 Hz, 4-H), 4.03 (dd, 1H, $J$ = 3.66, 6.96 Hz, 3-H), 4.66 (d, 1H, $J$ = 3.66 Hz, 2-H), 4.44—4.89 (m, 8H, Ph-$CH_2$), 7.21—7.37 (m, 20H, Ph). HRMS. (FAB) Found: *m/z* 508.2459. Calcd for $C_{33}H_{34}NO_4$: M+H$^+$, 508.2486.

**1-Azido-1,2-dibenzyloxyethane (4):** Colorless oil; IR (neat) 3030, 3000, 2840, 2100 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ = 3.64 (dd, 1H, $J$ = 5.50, 10.37 Hz, 2-Ha), 3.69 (dd, 1H, $J$ = 4.67, 10.45 Hz, 2-Hb), 4.60—4.64 (m, 4H, $PhCH_2$), 4.86 (d, 1H, $J$ = 11.82 Hz, 1-H), 7.28—7.36 (m, 10H, ArH). $^{13}$C NMR (128 MHz, $CDCl_3$) $\delta$ = 71.0, 71.1 (2×$PhCH_2$), 73.7 (2-C), 89.2 (1-C), 127.7—128.6 (Ph), 136.6, 137.5 (2×ipsoC of Ph). HRMS. (FAB, KI added)

Found: *m/z* 322.0955. Calcd for $C_{16}H_{17}N_3O_2K$: $M+K^+$, 322.0958.

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