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Thermolysis and Photolysis of Sugar Diazides

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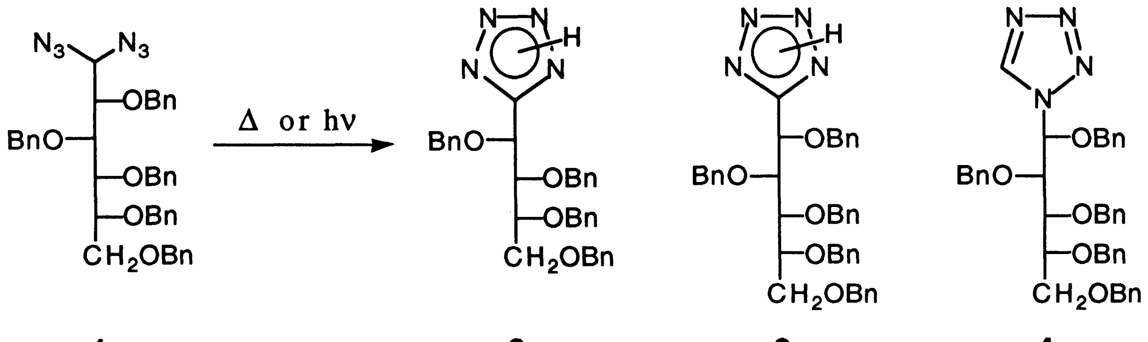
1,1-Diazido-2,3,4,5,6-penta-*O*-benzyl-D-glucose was refluxed in *o*-xylene under argon atmosphere to give 5-[(1'*R*,2'*S*,3'*R*-1',2',3',4'-tetrabenzyloxy)butyl]tetrazole in a high yield *via* an unpreceding rearrangement with one carbon shortening of sugar skeleton. In contrast its photolysis afforded two tetrazoles caused by the rearrangements without one carbon degradation; 5-[(1'*S*,2'*R*,3'*R*,4'*R*-1',2',3',4',5'-pentabenzyloxy)-pentyl]tetrazole and 1-[1'*R*,2'*S*,3'*R*,4'*R*-1',2',3',4',5'-pentabenzyloxy)pentyl]tetrazole.

Our investigation on sugar tetrazoles has shown that 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosylidene diazide is allowed to react in refluxing *o*-xylene to give the corresponding 7*R*,8*S*,9*S*,10*R*-8,9,10-tribenzyloxy-7-benzyloxymethyl-6-oxa-1,5-pentamethylenetetrazole *via* a ring-expansion in 82% yield.[1] As the extension of our study toward the synthesis of biologically active tetrazoles, we applied this reaction to the synthesis of tetrazoles bearing acyclic sugar moiety. In this study we found a new type of rearrangement reaction and wish to present herein the structure determination of rearranged products and a plausible reaction mechanism.

1,1-Diazido-2,3,4,5,6-penta-*O*-benzyl-D-glucose **1**[2] of a starting compound was prepared by the following four steps: Dithioketal formation, benzylation, dithioketal cleavage,[3] and diazide formation of D-glucose.[4] 1,1-Diazido-2,3,4,5,6-penta-*O*-benzyl-D-mannose **5** and 1,1-diazido-2,3,4,5-tetra-*O*-benzyl-D-arabinose **6** were also prepared by the same method as mentioned above. The thermal reaction of **1** was carried out as follows: A mixture of **1** (60 mg, 0.085 mmol) and *o*-xylene (3 ml) was refluxed for 6 h under argon atmosphere. After the solvent was evaporated under reduced pressure, the resulting residue was purified by the preparative TLC on silica gel (eluent: hexane / ethyl acetate = 2 / 1) to give 5-[(1'*R*,2'*S*,3'*R*-1',2',3',4'-tetrabenzyloxy)butyl]tetrazole **2**[5] as colorless needles (mp 155.0-155.5 °C) in 85% yield. The photochemical reaction of **1** was also performed as follows: A solution of **1** (130 mg, 0.186 mmol) in dichloromethane (10 ml) was irradiated with a high pressure mercury lamp (400 W) for 9 h at 30 °C. The resulting mixture was evaporated to give a yellow oil, which was then purified by the preparative TLC on silica gel (eluent: hexane / ethyl acetate = 2 / 1). 5-[(1'*S*,2'*R*,3'*R*,4'*R*-1',2',3',4',5'-Pentabenzyloxy)pentyl]tetrazole **3**[6] and 1-[(1'*R*,2'*S*,3'*R*,4'*R*-1',2',3',4',5'-pentabenzyloxy)pentyl]tetrazole **4**[7] were obtained as syrups in respective 29% and 22% yields together with the recovery **1** (6%).

Similarly, **5** was treated with the refluxing *o*-xylene to give **2** and 5-[(1'*R*,2'*S*,3'*R*,4'*R*-1',2',3',4',5'-pentabenzyloxy)pentyl]tetrazole **7**[8] in 15% and 29% yields, respectively. As an extension to the pentoses, **6** was refluxed in *o*-xylene for 11 h to afford 5-[(1'*S*,2'*R*-1',2',3'-tribenzyloxy)propyl]tetrazole **8**9) in 54% yield.

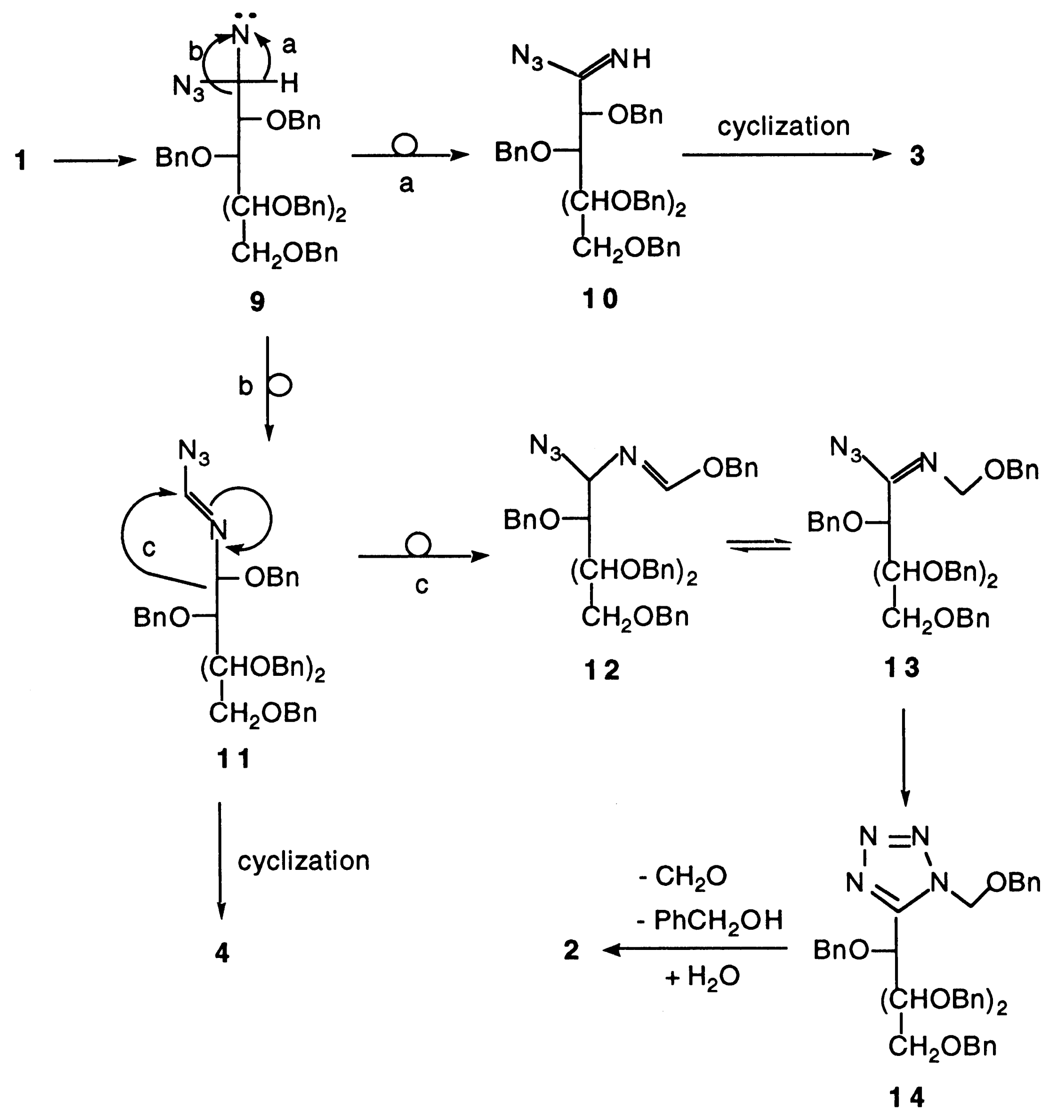


1 **2** **3** **4**

The structures of **2**, **3**, **4**, **7**, and **8** were determined by NMR and MS measurements together with elemental analysis: **2**: ^{13}C-NMR (COSY), 155.3 ppm (Cq, 5-C); ^{1}H-NMR, 1.65 ppm (NH disappeared with D_2O); MS *m/z* (FAB), 551 (M + 1)$^+$. **3**: ^{13}C-NMR (COSY), 153.8 ppm (Cq, 5-C); ^{1}H-NMR, 1.60 ppm (NH disappeared with D_2O); MS *m/z* (FAB), 671 (M + 1)$^+$. **4**: ^{13}C-NMR (COSY), 142.4 ppm (Ct, 5-C); MS *m/z* (FAB), 671 (M + 1)$^+$. **7**: ^{13}C-NMR (COSY), 154.0 ppm (Cq, 5-C); ^{1}H-NMR, 1.67 ppm (NH disappeared with D_2O); MS *m/z* (FAB), 671 (M + 1)$^+$. **8**: ^{13}C-NMR (COSY), 138.0 ppm (Cq, 5-C); ^{1}H-NMR, 12.74 ppm (NH disappeared with D_2O); MS *m/z* (FAB), 431 (M + 1)$^+$. In addition, the formation of **2** in the photolysis of **5** supported strongly the structure of sugar chain in **2** as 1'*R*, 2'*S*, 3'*R*-configuration which was the same as that of D-arabinose.

A plausible mechanism of this reaction is proposed as follows: **1** is heated in *o*-xylene to give an azidonitrene **9** with the evolution of nitrogen gas. Next, its C-2 carbon rearranges onto nitrogen atom *via* a path-b to afford **11**, which then undergoes the [1,3] sigmatropic shift *via* a path-c. The iminoazide derivative **13** thus formed is converted into the corresponding tetrazole **14**, which is quenched with water to give **2** accompanying with elimination of formaldehyde and benzylalcohol.10) In the case of photolysis, the anomeric-H of **9** shifts onto its nitrene as the hydride *via* a path-a. Thus obtained **10** undergoes an intramolecular 1,3-dipolar cycloaddition with azide group to give **3**. On the other hand, **11** derived from **9** undergoes this cyclization to afford **4**. The proposed intermediate **14** was also synthesized by the reaction of **2** with benzyl chloromethyl ether and then was converted into **2** again by refluxing in *o*-xylene. The reaction temperature was an important factor to cause the path-b rearrangement: **2** (58%) under refluxing *o*-xylene; **2** (16%) and **3** (38%) under heating *o*-xylene (130 °C); **3** (57%) under refluxing toluene.

In conclusion, we found a new kind of rearrangement in the thermolysis and photolysis of sugar diazides. Although the formation of **3** and **4** can be explained easily from the nitrene intermediate, it is not clear why **2** is formed *via* a [1,3] shift such as the path-c. The elucidation of the reaction mechanism may disclose a new chemistry. We have already found that 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosylidene diazide is irradiated with the high pressure mercury lamp to give the corresponding azidonitrene.1) However, Descotes *et al.* have recently reported that its acetyl derivative gives the corresponding anomeric carbene under the same conditions as above.11) Therefore the protective group may play an important role in the present reaction. Further investigation is undergoing in this laboratory to elucidate the reaction mechanism.



References

1) M. Yokoyama, M. Matsushita, S. Hirano, and H. Togo, *Tetrahedron Lett.*, **34**, 5097 (1993).

2) ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.66-3.70 (m, 2H, 6-H), 3.73-3.90 (m, 4H, 2, 3, 4, 5-H), 4.42-4.76 (m, 10H, $-OCH_2Ph$), 4.79 (d, 1H, 1-H, $J_{1,2}$ = 5.77 Hz), 7.12-7.34,(m, 25H, Ph). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 69.7 (6-C), 72.5, 73.2, 73.4, 75.2, 75.5 ($Ph\underline{C}H_2 \times 5$), 76.8, 77.4, 79.3, 79.4, 81.6 (1,2,3,4,5-C), 127.6-128.4 (Ph), 137.8, 137.9, 138.1, 138.1, 138.3 (ipso C of Ph×5). IR (neat) 3010 (Ph), 2850 (CH), 2100 (N_3) cm^{-1}. MS *m/z* (FAB), 699 $(M+1)^+$.

3) V. Pozsgay and H. J. Jennings, *J. Org. Chem.*, **53**, 4042, (1988).

4) J. -P. Praly, Z. El Kharraf, and G. Descotes, *J. Chem. Soc., Chem. Commun.*, **1990**, 431.

5) ^{1}H-NMR (400 MHz, CDCl$_3$): δ 1.65 (br, 1H, NH), 3.71 (dd, 1H, 4'-H, $J_{3',4'}$ = 3.66 Hz, J_{gem} = 10.81 Hz), 3.85 (dd, 1H, 4'-H, $J_{3',4'}$ = 2.75 Hz, J_{gem} = 10.81 Hz), 3.91-3.95 (m, 2H, 3'-H, 2'-OC$\underline{H}_2$Ph), 4.04 (dd, 1H, 2'-H, $J_{1',2'}$ = 3.12 Hz, $J_{2',3'}$ = 7.51 Hz), 4.31 (d, 1H, 4'-OC$\underline{H}_2$Ph, J_{gem} = 11.64 Hz), 4.35 (d, 1H, 4'-OC$\underline{H}_2$Ph, J_{gem} = 11.64 Hz), 4.38 (d, 1H, 2'-OC$\underline{H}_2$Ph, J_{gem} = 11.36 Hz), 4.46 (d, 1H, 1'-OC$\underline{H}_2$Ph, J_{gem} = 11.26 Hz), 4.53 (s, 2H, 3'-OC$\underline{H}_2$Ph), 4.66 (d, 1H, 1'-OC$\underline{H}_2$Ph, J_{gem} = 11.26 Hz), 5.36 (d, 1H, 1'-H, $J_{1',2'}$ = 3.11 Hz), 7.00-7.34 (m, 20H, Ph). ^{13}C-NMR (100 MHz, CDCl$_3$): δ 67.8 (4'-C), 72.0, 72.9, 73.5, 74.8 (Ph$\underline{C}H_2$×4), 72.4, 77.4, 79.7 (1', 2', 3'-C), 127.7-128.6 (Ph), 136.3, 136.7, 137.7, 137.8 (ipso C of Ph×4), 155.3 (5-C). IR (neat) 3000 (Ph), 2850 cm^{-1} (CH). **2** was also synthesized by the reaction of tetra-*O*-benzyl-D-arabinononitrile with ammonium azide.

6) ^{1}H-NMR (500 MHz, CDCl$_3$): δ 1.60 (br, 1H, NH), 3.73 (dd, 1H, 5'-H, $J_{4',5'}$ = 3.85 Hz, J_{gem} = 10.45 Hz), 3.87-3.90 (m, 2H, 4'-H, 5'-H), 4.17-4.27 (m, 3H, 2'-H, 3'-H, -OC$\underline{H}_2$Ph), 4.40-4.58 (m, 6H, -C$\underline{H}_2$Ph), 4.62 (d, 1H, -OC$\underline{H}_2$Ph, J_{gem} = 11.83 Hz), 4.68 (d, 1H, -OC$\underline{H}_2$Ph, J_{gem} = 6.87 Hz), 4.70 (d, 1H, -OC$\underline{H}_2$Ph, J_{gem} = 7.97 Hz), 5.28 (d, 1H, 1'-H, $J_{1',2'}$ = 6.05 Hz), 6.87-7.36 (m, 25H, Ph). ^{13}C-NMR (100 MHz, CDCl$_3$): δ 68.3 (5'-C), 70.9 (4'-C), 72.0, 72.6, 73.4, 74.3 (Ph$\underline{C}H_2$×4), 77.9, 78.4, 78.6 (1', 2', 3'-C), 127.8-128.6 (Ph), 136.5, 136.7, 137.2, 137.9, 138.1 (ipso C of Ph×5), 153.8 (5-C). IR (neat) 3000 (Ph), 2850 cm^{-1} (CH).

7) ^{1}H-NMR (270 MHz, CDCl$_3$): δ 3.59 (dd, 1H, 5'-H, $J_{4',5'}$ = 4.1 Hz, J_{gem} = 9.9 Hz), 3.68 (dd, 1H, 5'-H, $J_{4',5'}$ = 4.3 Hz, J_{gem} = 9.9 Hz), 3.80-3.88 (m, 2H, 3'-H, 4'-H), 3.97 (dd, 1H, 2'-H, $J_{1',2'}$ = 4.3 Hz, $J_{2',3'}$ = 6.5 Hz), 4.18 (d, 1H, -OC$\underline{H}_2$Ph, J_{gem} = 11.0 Hz), 4.30-4.61 (m, 6H, -OC$\underline{H}_2$Ph, J_{gem} = 11.6 Hz), 4.64-4.67 (m, 3H, OC$\underline{H}_2$Ph), 6.20 (d, 1H, 1'-H, $J_{1',2'}$ = 4.3 Hz), 7.03-7.34 (m, 25H, Ph), 8.56 (s, 1H, 5-H). ^{13}C-NMR (126 MHz, CDCl$_3$): δ 68.1 ($\underline{C}H_2OBn$), 72.0, 72.3, 73.4, 74.5, 75.7 (Ph$\underline{C}H_2$×5), 77.7, 78.6, 80.1, 87.9 (1', 2', 3', 4'-C), 127.7-128.7 (Ph), 135.0, 136.9, 137.8, 137.8, 138.1 (ipso C of Ph×5), 142.4 (5-C). IR (neat) 3010 (Ph), 2850 cm^{-1} (CH).

8) ^{1}H-NMR (400 MHz, CDCl$_3$): δ 1.67 (br, 1H, NH), 3.73 (dd, 1H, 5'-H, $J_{4',5'}$ = 3.67 Hz, J_{gem} = 10.08 Hz), 3.85-3.91 (m, 2H, 5'-H, -OC$\underline{H}_2$Ph), 4.17-4.25 (m, 3H, 2'-H, 3'-H, 4'-H), 4.40-4.47 (m, 2H, -OC$\underline{H}_2$Ph), 4.52-4.70 (m, 7H, -OC$\underline{H}_2$Ph), 5.28 (d, 1H, 1'-H, $J_{1',2'}$ = 5.87 Hz), 6.88-7.35 (m, 25H, Ph). ^{13}C-NMR (100 MHz, CDCl$_3$): δ 68.4 (5'-C), 71.1 (4'-C), 72.0, 72.6, 73.4, 74.4, 74.6 (Ph$\underline{C}H_2$×5), 78.0, 78.5, 78.7 (1', 2', 3'-C), 127.7-128.6 (Ph), 136.5, 136.8, 137.2, 138.0, 138.2 (ipso C of Ph×5), 154.0 (5-C). IR (neat) 3000 (Ph), 2850 cm^{-1}(CH).

9) ^{1}H-NMR (500 MHz, CDCl$_3$): δ 3.43 (dd, 1H, 3'-H, $J_{2',3'}$ = 6.23 Hz, J_{gem} = 10.12 Hz), 3.50 (dd, 1H, 3'-H, $J_{2',3'}$ = 4.86 Hz, J_{gem} = 10.12 Hz), 4.16 (ddd, 1H, 2'-H, $J_{1',2'}$ = 3.12 Hz, $J_{2',3'}$ = 4.86, 6.23 Hz), 4.40 (d, 1H, 1'-OC$\underline{H}_2$Ph, J_{gem} = 11.84 Hz), 4.44 (d, 1H, 1'-OC$\underline{H}_2$Ph, J_{gem} = 11.84 Hz), 4.49 (d, 1H, 2'-OC$\underline{H}_2$Ph, J_{gem} = 11.72 Hz), 4.54 (d, 1H, 2'-OC$\underline{H}_2$Ph, J_{gem} = 11.72 Hz), 4.69 (d, 1H, 3'-OC$\underline{H}_2$Ph, J_{gem} = 6.47 Hz), 4.72 (d, 1H, 3'-OC$\underline{H}_2$Ph, J_{gem} = 6.47 Hz), 5.17 (d, 1H, 1'-H, $J_{1',2'}$ = 3.12 Hz), 7.17-7.36 (m, 15H, Ph), 12.74 (br, 1H, NH). ^{13}C-NMR (100 MHz, CDCl$_3$): δ 68.4 (3'-C), 71.9 (2'-C), 72.1 (3'-OCH$_2$Ph), 73.6 (1' and 2'-OCH$_2$Ph), 78.8 (1'-C), 127.6-128.9 (Ph×3), 136.7, 136.7, 137.3 (ipso C of Ph×3), 138.0 (5-C). IR (KBr) 3040 (Ph), 2880 cm^{-1}(CH).

10) The benzylalcohol was detected by GC-MS (Shimadzu GCMS-QP-2000A) in ca. 60% yield based on **2**.

11) J. -P. Praly, C. Di Stefano, G. Descotes, and R. Faure, *Tetrahedron Lett.*, **35**, 89 (1994).

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