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A CONVENIENT ONE-POT PREPARATION OF GLYCOSYL BROMIDES AS WELL AS GLYCOSYL ACETATES FROM BENZYL GLYCOSIDES USING N-BROMOSUCCINIMIDE.

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Summary: Some conversions of benzyl glycoside using NBS were examined and one-pot preparation of glycosyl acetates and bromides were developed. An efficient O-debenzylation at non-anomeric position was also observed.

Benzyl group has been frequently used for protection of hydroxyl group especially in the field of carbohydrates. In the course of synthetic studies on glycocinnamoylspermidine, a selective debenzylation of benzyl 2-azido-2-deoxy-α-D-xylopyranoside derivatives such as 1-4[1] was required in the presence of azido as well as carbamate groups. In this case the generally used hydrogenolytic deprotection is inadequate. Furthermore, neither acid hydrolysis nor acetolysis[1] proved to be applicable for these compounds. In this communication we would like to describe a convenient and one-pot conversions of benzyl glycoside into the corresponding bromide as well as acetate.

It is well known[2] that benzyl alkyl ether reacts with N-bromosuccinimide (NBS) to give benzaldehyde via α-bromination. This reaction was applied to benzyl protecting group, especially at the anomeric center, of carbohydrates and it was found that reaction of benzyl glycoside with NBS followed by various treatment provided several efficient conversions, which are summarized in the following scheme and Table. Treatment of benzyl 2-azido-2-deoxy-β-L-

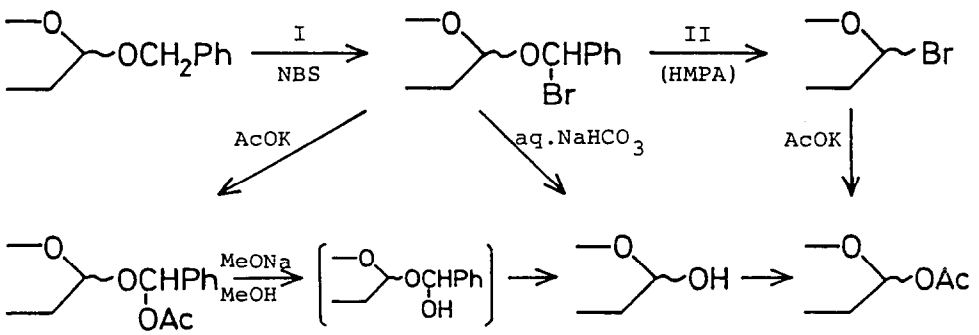
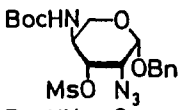
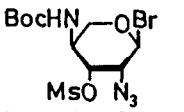
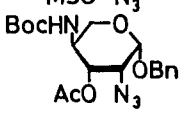
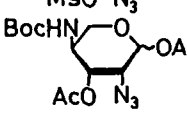
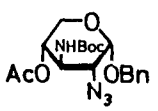
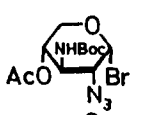
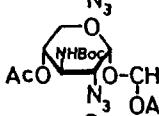
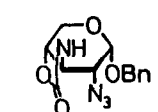
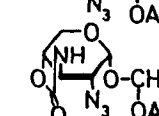
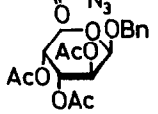
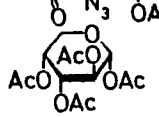
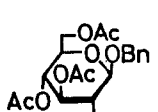
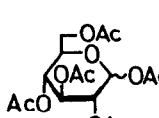


Table. Some Chemical Conversions of Benzyl Glycosides via Bromination with NBS

Entry	Benzyl glycoside[4]	Method[a]	Reaction time[b]	Product[5]	Yield %
1	 (1)	A	3 h	 (7)	81
2	 (2)	B	1) 0.5 h 2) 3.5 h	 (8)	61
3	2	C	1) 0.5 h 2) 2 h	8[c]	60
4	 (3)	D	1) 10 min 2) 5 min	 (9)	85
5	3	E	12 h	 (10)[d]	87
6	 (4)	E	12 h	 (11)[d]	81
7	 (5)	F	1) 22 h 2) 4 h	 (12)	81 (14)[e]
8	5	G	1) 15 min 2) 1 h 3) 1.5 h	12	85 (6)[e]
9	 (6)	G	1) 15 min 2) 1.5 h 3) 1.5 h	 (13)	83 (8)[e]

a) A: NBS (1.5 equiv), $BaCO_3/CCl_4$;
B: 1) NBS (3 equiv) /CCl_4, 2) AcONa (10 equiv) /AcOH;
C: 1) NBS (1.5 equiv), $BaCO_3/CCl_4$, 2) AcONa (10 equiv) /AcOH;
D: 1) NBS (2.7 equiv), $BaCO_3/CCl_4$, 2) HMPA (0.4 equiv);
E: NBS (3 equiv), $(PhCO)_2O_2$ (0.08 equiv), AcOK (8.8 equiv) /$CHCl_3$-CCl_4 (1:1);
F: 1) NBS (3 equiv), $BaCO_3/CCl_4$, 2) AcOK (10 equiv);
G: 1) NBS (1.4 equiv), $BaCO_3/CCl_4$, 2) HMPA (1 equiv), 3) AcOK (10 equiv) /AcOH

b) For each step described in the method.

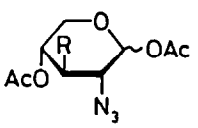
c) The ratio of α- and β-anomers was 3 to 1.

d) Obtained as an epimeric mixture at the benzylic position with a ratio of 3 to 2.

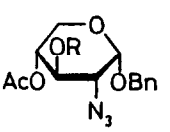
e) Recovered benzyl glycoside.

lyxopyranoside derivative (1) with NBS in refluxing carbon tetrachloride gave the corresponding glycosyl bromide in good yield (entry 1). Formation of glycosyl bromide from benzyl glycoside may consist of two steps, that is, benzylic bromination (step I) and rearrangement (step II). The step I may proceed rapidly via radical mechanism as generally accepted. Barium carbonate was added in order to prevent some side reactions caused by acidic by-products, but seems to be not necessary as shown in entry 2. The step II has presumably an ionic mechanism and needs heating for 3-22 h. The relative high reactivity of 1 and 2 may attributed to the instability of the starting compound caused by 1,3-diaxial interaction. A remarkable effect of HMPA (1 equiv) for acceleration of this step was observed (entry 4: the second step of the method D), and proved to be generally utilized for the formation of glycosyl bromide from such benzyl glycoside as 5 and 6 (entries 8 and 9: the second step of the method G). Glycosyl bromide was further converted into the corresponding acetate with sodium or potassium acetate/acetic acid (entries 2, 3, 8 and 9: the second step of the method B and C, and the third step of the method G). Moreover, if the reaction is carried out in the presence of potassium acetate α-bromo intermediate could be trapped as the corresponding α-acetoxy derivative (entries 5 and 6). Although in this reaction, chloroform was used as a cosolvent, a radical initiator such as dibenzoyl peroxide seems to be effective for promoting the reaction. An α-acetoxy derivative (10) was further converted into glycosyl acetate (14) by treatment with sodium methoxide followed by conventional acetylation. Typical procedure for conversion of benzyl glycoside into glycosyl acetate is as follows: A mixture of benzyl glycoside (1 mmol) and barium carbonate (0.5 mmol) in carbon tetrachloride (6 ml) was heated under reflux for 20 min. To this mixture was added, with stirring, NBS (1.4 mmol) and then after 10-15 min HMPA (1 mmol), and heating was continued for 1.5 h. Addition of potassium acetate (10 mmol) and acetic acid (2.5 ml), and further heating for 1.5 h followed by conventional workup gave glycosyl acetate.

A further aspect of this reaction was observed in the case of benzyl 4-O-acetyl-2-azido-3-O-benzyl-2-deoxy-α-D-xylopyranoside (17). When NBS (1 equiv) was added portionwise to a solution of 17 in carbon tetrachloride under reflux, two kinds of partically O-debenzylated derivatives, 18 and 15, was obtained in 50% and 14% yields, respectively, together with totally O-debenzylated one (16) in 14% yield. Furthermore, the last compound could be prepared quantitatively by treatment with NBS and catalytic amount of bromine



14 R=NHBoc
15 R=OBn
16 R=OAc



17 R=Bn
18 R=Ac

at room temperature for 19 h (induction time was observed), followed by hydrolysis of α-bromide with aqueous sodium hydrogencarbonate and then by conventional acetylation.

As the reaction of benzylidene acetal with NBS has been widely used for its conversion into sugar bromobenzoate[6], chemical conversions of benzylated carbohydrate using NBS described in this letter could provide a new aspect in synthetic chemistry of carbohydrates.

References and Notes

1. H. Hashimoto, M. Kawa, Y. Saito, T. Date, and J. Yoshimura, Carbohydr. Res (in contribution).
2. a) R. L. Huang and K. H. Lee, J. Chem. Soc., 1964, 5957. b) J. S. Pizey, "N-Bromosuccinimide" in "Synthetic Reagents", John Wiley & Sons, New York (1974), p1.
3. K. Araki, M. Kawa, Y. Saito, H. Hashimoto, and J. Yoshimura, Bull. Chem. Soc. Jpn., 59, 3137 (1986).
4. Compound 1–4 will be reported in the contributed paper[1], while 14–17 were reported previously[3].
5. New glycosyl bromides 7 and 9 could be characterized only by ^{1}H-NMR data (100 MHz in $CDCl_3$).
   7: δ 6.33 (d, $J_{1,2}$=1.0 Hz, H-1), 4.46 (dd, $J_{2,3}$=3.0 Hz, H-2), 5.44 (dd, $J_{3,4}$=7.0 Hz, H-3), 3.14 (s, Ms), 1.45 (s, t-Bu).
   9: δ 6.45 (d, $J_{1,2}$=3.0 Hz, H-1), 2.10 (s, Ac), 1.46 (s, Boc).
   Other new compounds 8, 10, and 11 gave satisfactory elemental analysis and spectral data.
   8: ^{1}H-NMR ($CDCl_3$): δ 6.00 (d, $J_{1,2}$=3.5 Hz, H-1α), 5.93 (d, $J_{1,2}$=2.5 Hz, H-1β), 5.33 (dd, $J_{2,3}$=3.5 Hz, $J_{3,4}$=8.5 Hz, H-3α), 5.22 (dd, $J_{2,3}$=3.0 Hz, $J_{3,4}$=8.0 Hz, H-3β), 4.74 (bd, J=8.0 Hz, NH), 2.16 (s, Ac), 1.44 (s, t-Bu).
   10: $[\alpha]_D^{25}$ +135° (c=1.1, $CHCl_3$, 1:1 mixture of two epimers); ^{1}H-NMR ($CDCl_3$) δ 5.48 (d, $J_{1,2}$=3.6 Hz, H-1a), 5.19 (d, $J_{1,2}$=3.2 Hz, H-1b), 4.90 (dt, $J_{3,4}$=10.1 Hz, $J_{4,5}$=10.3 Hz, $J_{4,5'}$=5.8 Hz, H-4a), 4.96 (dt, $J_{3,4}$=$J_{4,5}$=9.5 Hz, $J_{4,5'}$=6.1 Hz, H-4b), 6.87 (s, PhCHa), 6.99 (s, PhCHb), 2.03 and 2.17 (each s, OAca), 2.10 and 2.15 (each s, OAcb), 1.47 (s, t-Bu).
   11: $[\alpha]_D^{25}$ +171.4° (c=1.8, $CHCl_3$, 3:2 mixture of two epimers); ^{1}H-NMR ($CDCl_3$): δ 5.25 (d, $J_{1,2}$=3.4 Hz, H-1a), 5.57 (d, $J_{1,2}$=3.6 Hz, H-1b), 6.95 (s, PhCHa), 6.85 (s, PhCHb), 2.14 (s, OAca), 2.15 (s, OAcb), 6.29 (bs, NH)
6. J. Gelas, Adv. Carbohydr. Chem. Biochem., 39, 71 (1981).

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