Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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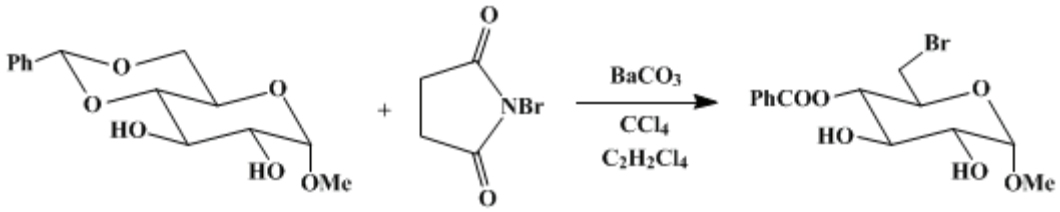
6-BROMO-6-DEOXY HEXOSE DERIVATIVES BY RING OPENING OF BENZYLIDENE ACETALS WITH *N*-BROMOSUCCINIMIDE: METHYL 4-*O*-BENZOYL-6-BROMO-6-DEOXY-α-D-GLUCOPYRANOSIDE

[Glucopyranoside, methyl 6-bromo-6-deoxy-, 4-benzoate, α-D-]



Submitted by S. Hanessian[1]
Checked by Janice Cammack and James D. White.

1. Procedure

To a suspension containing 20.5 g (72.61 mmol) of methyl 4,6-O-benzylidene-α-D-glucopyranoside (Note 1) in 1 L of carbon tetrachloride and 60 mL of 1,1,2,2-tetrachloroethane (Note 2) are added 15 g (84.27 mmol) of *N*-bromosuccinimide and 8 g (31.13 mmol) of barium carbonate (Note 3). The resulting suspension is heated at the reflux temperature of the mixture with mechanical stirring for a 2.5-hr period and filtered while hot. During the initial period of heating, a reddish orange color develops but fades before termination of the reaction. The yellowish gummy residue in the flask is washed with two 100-mL portions of hot carbon tetrachloride and the filtrate and washings are evaporated under reduced pressure to give a pale-yellow oil that is dissolved in 500 mL of ether. The solution is washed with three 60-mL portions of water, then dried over anhydrous sodium sulfate. Evaporation affords a pale-yellow oil that crystallizes (Note 4) on trituration with cold ether to yield 12.1 g of white crystals, mp 120–123° C. A second crop of 1.72 g is obtained from the mother liquors (Note 5). Recrystallization of 1 g of product by dissolution in a minimum volume of acetone and addition of ether, then pentane gives 0.9 g of white crystals, mp 131–132°C; $[\alpha]_D$ + 118° ($CHCl_3$, *c* 1).

2. Notes

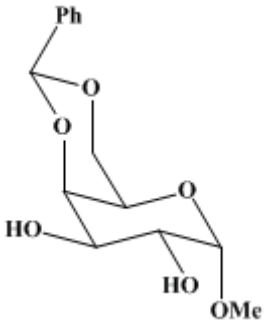
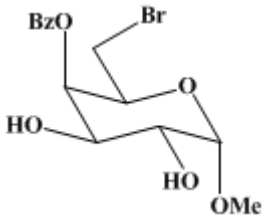
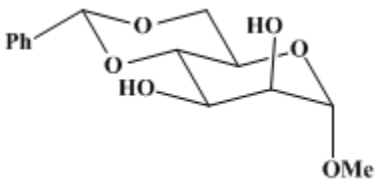
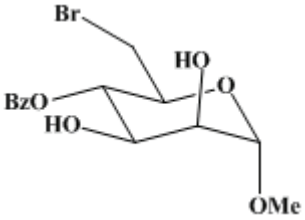
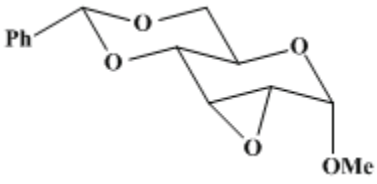
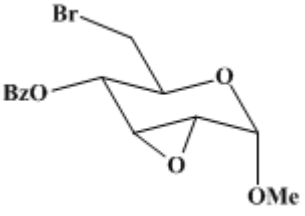
1. The preparation of methyl 4,6-O-benzylidene-α-D-glucopyranoside follows essentially the procedure reported.[2] A mixture of 60 g (0.31 mol) of methyl α-D-glucopyranoside, 45 g of freshly fused and powdered zinc chloride, and 150 mL of benzaldehyde ("practical" grade) is stirred at room temperature for a period of 48 hr. The resulting pale-yellow, cloudy reaction mixture is poured slowly, with stirring, into 1.25 L of cold water, stirred for an additional 10 min, and refrigerated overnight. Hexane (75 mL) is added and the resulting mixture is stirred for 0.5 hr to aid in removing excess benzaldehyde. The product is separated on a Büchner funnel, washed twice with 100 mL of cold water, and dried under vacuum at room temperature overnight. Recrystallization from chloroform–ether affords 55 g (63% yield) of analytically pure material, mp 164–165°C.
2. Carbon tetrachloride (spectral grade) was passed through a thick layer of Woelm alumina (neutral). 1,1,2,2-Tetrachloroethane was used as a cosolvent to aid in the dissolution of the starting sugar derivative. In other instances carbon tetrachloride was the solvent.
3. Barium carbonate can be replaced by calcium carbonate in some cases; see Chretien, F.; Khaldi, M.; Chapleur, Y. *Syn. Commun.*, **1990**, *20*, 1589.
4. Crystallization did not occur if traces of tetrachloroethane were present. The checkers found it necessary to evaporate at ~0.05 mm in a warm water bath for ca. 2 hr to remove residual solvent.
5. Evaporation of the mother liquors and flash-column chromatography (350 mL of silica gel; column height 28 cm; eluant 70% ethyl acetate–hexanes, fraction size, 30 mL), given additional (1.87 g) product

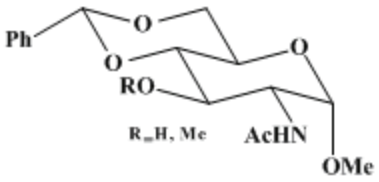
that was eluted with fractions 25–36; total yield 15.69 g, (Silica gel, Kieselgel 60; E. Merck AG, Darmstadt, Germany.)

3. Discussion

Halogeno sugar derivatives are versatile intermediates for the preparation of aminodeoxy, deoxy, thio, and related analogs.[3] These transformations are easily achieved in the case of primary halides, which in turn can be prepared by a variety of methods. A number of 6-deoxy and 6-amino-6-deoxy hexoses are components of antibiotics and related natural products.[4,5] Benzylidene acetals of the 1,3-dioxane or 1,3-dioxolane type undergo a ring-opening reaction in the presence of *N*-bromosuccinimide to give the corresponding *O*-benzoylated bromohydrins.[6] This transformation has been known for a number of years in the carbohydrate series (Hanessian–Hullar reaction),[7] and has been used extensively in synthetic work. In the case of 4,6-*O*-benzylidene acetals, the products are the 6-bromo-6-deoxy-4-benzoates. Internal acetals of the 1,3-dioxolane type often undergo ring opening to give the two possible regioisomeric bromo benzoates. The reaction is compatible with a variety of functional and protecting groups (ester, ether, amide, halide, epoxide, etc.). It is also applicable to substrates containing free hydroxyl groups such as the example given above. A unique feature, which arises as a consequence of the nature of the ring opening, is seen in the case of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside and its derivatives. In this series the benzoate group is found at the C-4 position which has an axial orientation. Hence one achieves halogenation at the primary position as well as an indirect benzoylation of an axial hydroxyl group in the parent sugar. Other applications have been found in amino sugars and nucleosides. Table I illustrates a selection of such ring-opening reactions. The reaction has also been applied with disaccharide acetals.[6,8]

TABLE I
REACTION OF *O*-BENZYLIDENE ACETALS WITH *N*-BROMOSUCCINIMIDE

Starting Acetal	Product(s)	Reference
		5
		5
		5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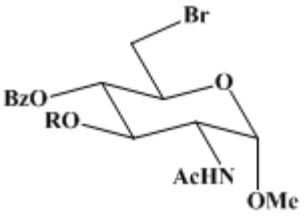
O
O
RO
R=H, Me
AcHN
OMe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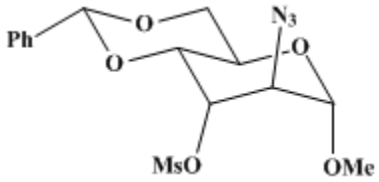
BzO
RO
O
AcHN
OMe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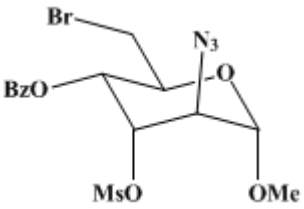
O
N3
O
MsO
OMe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O
MsO
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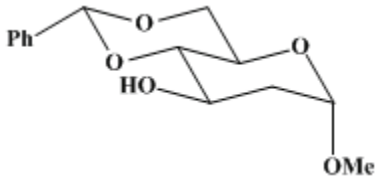
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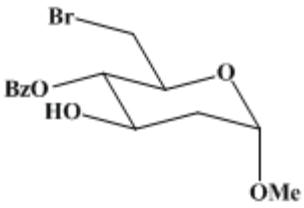
O
O
HO
OMe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O
HO
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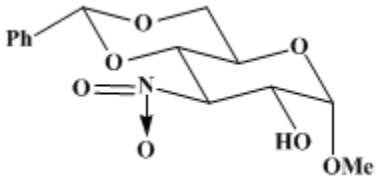
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O
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N
O
HO
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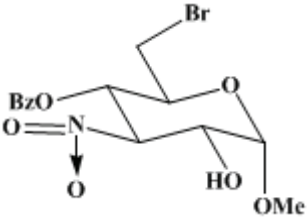
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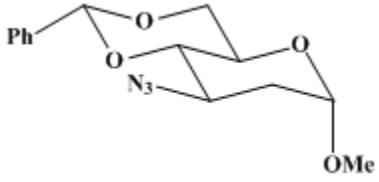
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O
O
N3
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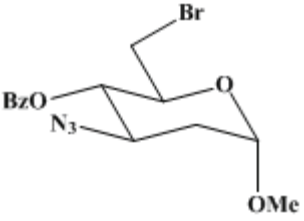
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N3
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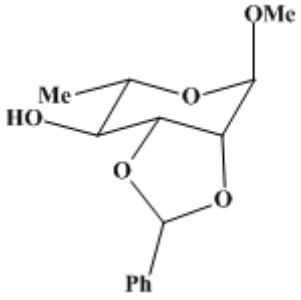
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Me
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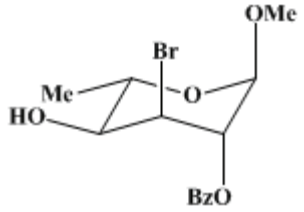
HO
O
O
Ph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HO
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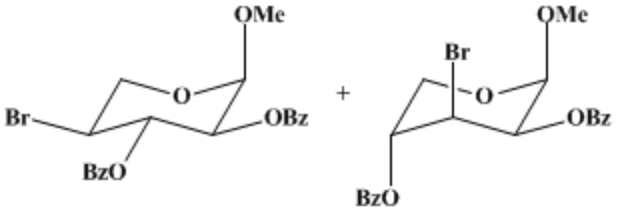
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OBz
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+
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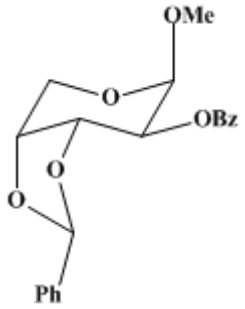
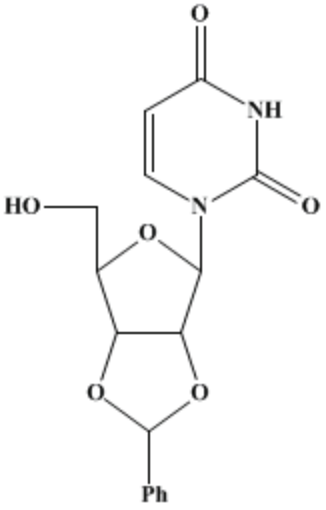
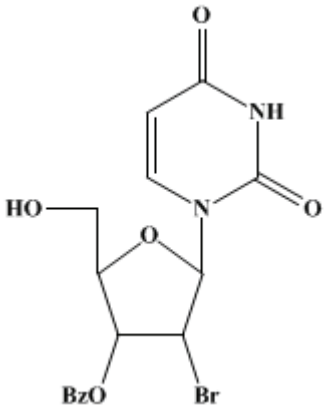
O
OBz
BzO







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References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

silica gel

Glucopyranoside, methyl 6-bromo-6-deoxy-, 4-benzoate, α-D-

hexanes

ethyl acetate (141-78-6)

ether (60-29-7)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

benzaldehyde (100-52-7)

calcium carbonate (471-34-1)

acetone (67-64-1)

zinc chloride (7646-85-7)

barium carbonate (513-77-9)

Pentane (109-66-0)

tetrachloroethane (630-20-6)

N-bromosuccinimide (128-08-5)

hexane (110-54-3)

1,1,2,2-tetrachloroethane (79-34-5)

Methyl 4-O-benzoyl-6-bromo-6-deoxy-α-D-glucopyranoside (10368-81-7)

Methyl 4,6-O-benzylidene-α-D-glucopyranoside (3162-96-7)

methyl α-D-glucopyranoside (97-30-3)

methyl 4,6-O-benzylidene-α-D-galactopyranoside