CHEMISTRY LETTERS, pp. 289-292, 1983.

A CONVENIENT METHOD FOR THE PREPARATION OF 4,6-O-BENZYLIDENEGLYCALS FROM METHYL 2,3-ANHYDRO-4,6-O-BENZYLIDENE-α-D-HEXOPYRANOSIDES[1)]

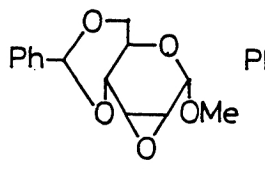
Nobuo TSUDA, Sumio YOKOTA, Takashi KUDO, and Oyo MITSUNOBU*
Department of Chemistry, College of Science and Engineering,
Aoyama Gakuin University, Chitosedai, Setagayaku, Tokyo 157

The reaction of methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside (1) with ethylmagnesium bromode in the presence of CuI afforded 4,6-O-benzylidene-1,2-dideoxy-D-ribo-hex-1-enopyranoside (2). Similarly, methyl 2,3-anhydro-4,6-O-benzylidene-α-D-gulopyranoside (6) gave 4,6-O-benzylidene-1,2-dideoxy-D-xylo-hex-1-enopyranoside (7).

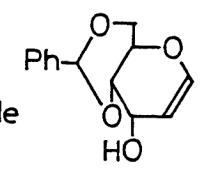
Carbohydrates have been utilized as starting materials in synthesis of chiral natural products.[2)] In spite of major advances in this synthetic methodology reported in recent years, there still exists an ongoing need to develop convenient procedure for the transformation of carbohydrates into activated forms.

In hexopyranoside, the hydroxyl group at the C-6 position can be selectively protected or functionalized, while sharp discrimination between hydroxyl groups at C-2, C-3, and C-4 positions is difficult because they exhibit similar reactivity.[3)] 2,3-Anhydropyranosides are therefore considered to be potential intermediates provided that the oxirane-ring cleaves in a regioselective manner. This is actually the case in locked 2,3-anhydropyranoside system.[4)] Thus, methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside (1) reacts with a variety of organometallic reagents to give the corresponding 2-deoxy-2-substituted altropyranosides.[5)]

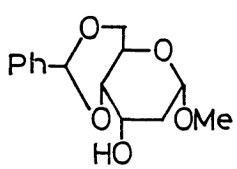
On the other hand, the reaction of 1 with Grignard reagents affords a mixture of products, despite the main reaction site is again the C-2 position. For example, Inch and Lewis have reported that the reaction of 1 with methylmagnesium iodide resulted in the formation of 4,6-O-benzylidene-1,2-dideoxy-D-ribo-hex-1-enopyranoside (2), methyl 4,6-O-benzylidene-2-deoxy-D-ribo-α-hexopyranoside (3), and methyl 4,6-O-benzylidene-3-deoxy-3-iodo-α-D-glucopyranoside (4a) in 44%, 20%, and 4.5% yields, respectively.[6)]



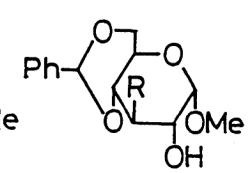
1



2



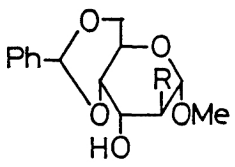
3



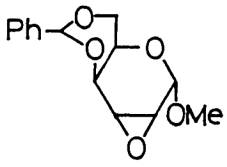
4a R=I
b R=Et

In connection with our interest in the reaction of anhydrosugars, we sought to control the course of the Grignard reaction to produce single product. At the outset, in order to activate the oxirane-ring,[7] the reaction of 1 (1 mmol) with ethylmagnesium bromide (5 mmol) was carried out in the presence of triisobutylalminium (1.5 mmol; THF, -78 °C~room temperature, 20 h), where 2, 3, and methyl 4,6-O-benzylidene-2-bromo-2-deoxy-α-D-altropyranoside (5a) were obtained in 23%, 59%, and 11% yields, respectively. As a control experiment, 1 (1 mmol) was allowed to react with ethylmagnesium bromide (10 mmol; THF, room temperature, 20 h) to give 2 and 3 in 65% and 27% yields, respectively.[8] These results indicate that triisobutylalminium facilitates the reduction of 1.

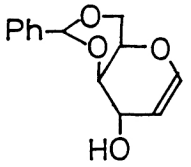
In view of regioselectivity attained in the reaction of 1 with lithium dimethylcuprate,[5a] 1 (2.5 mmol) was allowed to react with ethylmagnesium bromide (10 mmol) in the presence of CuI (0.3 mmol; THF, -20 °C~room temperature, 5 h) giving 2, methyl 4,6-O-benzylidene-3-deoxy-3-C-ethyl-α-D-glucopyranoside (4b), and methyl 4,6-O-benzylidene-2-deoxy-2-C-ethyl-α-D-altropyranoside (5b) in 70%, 22%, and 7% yields, respectively. When the amount of CuI was increased to 25% with respect to 1, the yield of 2 was increased to 85%.[9]



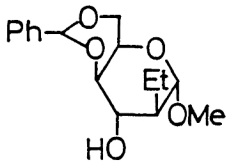
5a R=Br
b R=Et



6



7

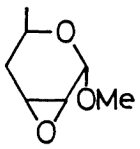


8

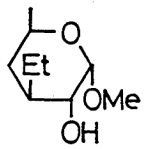
It has been assumed that 2 and 3 arise from the reaction of initially formed 5 (R = Br, I) with excess Grignard reagent.[6] Thus 5a was treated with ethylmagnesium bromide to give 2 and 3 in 36% and 61% yields, respectively. When the reaction was carried out in the presence of CuI, the yield of 2 was increased to 85%, and 3 was obtained in 10% yield. These results indicate that CuI suppresses the reduction process and/or facilitates the elimination reaction.

Methyl 2,3-anhydro-4,6-O-benzylidene-α-D-gulopyranoside (6) was also reacted with ethylmagnesium bromide in the presence of CuI to afford 4,6-O-benzylidene-1,2-dideoxy-D-xylo-hex-1-enopyranoside (7) and methyl 4,6-O-benzylidene-2-deoxy-2-C-ethyl-α-D-idopyranoside (8) in 75% and 16% yields, respectively.

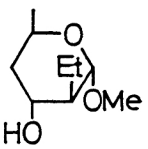
Contrary to the cases of locked 2,3-anhydro-α-D-hexopyranosides, the reaction of methyl 2,3-anhydro-4,6-dideoxy-α-D-allopyranoside (9; 2.5 mmol) with ethylmagnesium bromide (12.4 mmol) in the presence of CuI (0.74 mmol; THF, 0 °C, 3 h) resulted in the formation of a mixture of products from which methyl 3,4,6-trideoxy 3-C-ethyl-D-xylo-α-hexopyranoside (10; 14%) and methyl 2,4,6-trideoxy-2-C-ethyl-D-arabino-α-hexopyranoside (11; 7%) could be isolated.



9



10



11

Glycals have been utilized as versatile starting materials for carbohydrates synthesis and, in recent years, for natural products synthesis. Lemieux and his coworkers have reported a two-step procedure for the preparation of 2 and 7 from 1 and 6.[10] The method described in this paper provides a one-step procedure for the preparation of 4,6-O-benzylidenepyranoside glycals.

Typical experimental procedures: Reaction of 6 with ethylmagnesium bromide in the presence of CuI. A solution of ethylmagnesium bromide prepared from 123 mg (5.0 mmol) of Mg and 567 mg (5.2 mmol) of ethyl bromide in THF (3 ml) was added dropwise to CuI (50 mg, 0.26 mmol) in THF (1 ml) at -23 °C under N_2. To the mixture was added a solution of 6 (267 mg, 1.01 mmol) in THF (12 ml) at 0 °C. The mixture was stirred at room temperature for 30 min and then refluxed for 3 h. The mixture was cooled in an ice bath, saturated aqueous NH_4Cl (10 ml), dil HCl (1 ml), and chloroform (10 ml) being successively added. After filtration, organic layer was separated and water solution extraced with chloroform (30 ml × 3). The collected organic layers were dried (Na_2SO_4) and evaporated. The residue was applied to silica gel plates and developed by chloroform-ethyl acetate (10 : 1) giving 7 (75%, 177 mg) and crude 8. Compound 7 was recrystallized from ethanol, mp 131-132 °C; lit[10] mp 128.5-129.5 °C. Crude 8 was rechromatographed (chloroform-ethyl acetate = 20 : 1) to give pure 8 (47 mg, 16%) which was recrystallized from ethanol, mp 124.5-125.5 °C. Found: C, 65.28; H, 7.52%. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.52%.

Reaction of 5a with ethylmagnesium bromide in the presence of CuI. A solution of ethyl magnesium bromide prepared from 75 mg (3.1 mmol) of Mg and 349 mg (3.2 mmol) of ethyl bromide in THF (3 ml) was added dropwise to CuI (26.1 mg, 0.14 mmol) in THF (1 ml) at -20 °C under Ar and the reaction was maintained at this temperature for 15 min. To the mixture was added a solution of 5a (174 mg, 0.5 mmol) in THF (5 ml) at 0 °C. The mixture was stirred for 2 h at 0 °C and then for 6 h at room temperature. The reaction was stopped by the addition of saturated aqueous NH_4Cl. After concentration, the residue was extracted with chloroform. Organic layer was dried (Na_2SO_4) and evaporated. The residue was applied to silica gel plates and developed by petroleum ether-ether (3 : 2) to give 2 (100 mg, 85%, mp 82 °C; lit[10] mp 83.5 °C) and 3 (13 mg, 10%, mp 131-133 °C; lit[6] mp 127-128 °C).

This work was supported in part by a Grant-in Aid for Scientific Research from Ministry of Education, Science and Culture.

References

1) Stereospecific and Stereoselective Reactions. VII. For Part VI, see O. Mitsunobu, M. Ebina, and T. Ogihara, Chem. Lett., 1982, 373. This work has been presented in part at 43th Meeting of Chemical Society of Japan, April 2, 1981, "Abstracts of Paper" 4F13.

2) The use of carbohydrates as starting materials for the constraction of chiral natural products has been reviewed. See for example, S. Hanessian, Acc. Chem. Res., 12, 159 (1979); A. Vasella, in "Modern Synthetic Methods, 1980", R. Scheffold, ed., Otto Salle Verlag-Verlag Sauerlander (1980), pp 163-267; Y. Nakahara and T. Ogawa, in "Kosentakuteki Hanno", H. Nozaki, T. Mukaiyama, and

R. Noyori, ed., Kagakudozin, Kyoto (1980), pp 101-116; H. Ohrui, Yuki Gosei Kagaku Kyokai Shi, 39, 275 (1981).

3) For a review of relative reactivities of hydroxyl groups in carbohydrates, see A. H. Hains, in "Advances in Carbohydrate Chemistry and Biochemistry", P. S. Tipson and D. Horton, ed., Academic Press, New York (1976), Vol. 33, pp 11-109. Recentry Ishido and coworkers have reported selective removal of 2-O-acetyl group of fully acylated methyl glycosides; Y. Ishido, N. Sakairi, M. Sekiya, and N. Nakazaki, Carbohydr. Res., 97, 51 (1981) and refs. therein; see also Y. Ishido and N. Sakairi, ibid., 97, 151 (1981).

4) R. D. Guthrie, in "The Carbohydrates, Chemistry and Biochemistry (2nd Ed.)", W. Pigman and D. Horton, ed., Academic Press, New York (1972), Vol. IA, pp 423-478; J. G. Buchanan and H. Z. Sable, in "Selective Organic Transformation", B. S. Thyagarajan, ed., Wiley-Interscience, New York (1972), Vol. 2, pp 1-95.

5) For example, a) Lithium dimethylcuprate; D. R. Hicks and B. Fraser-Reid, Can. J. Chem., 53, 2017 (1975). b) Sodiomethyl methyl sulfoxide; M. Sharma and R. K. Brown, ibid., 46, 757 (1968). c) Dimethyl sodiomalonate; S. Hanessian and P. Dextraze, ibid., 50, 226 (1972). d) 2-Lithio-1,3-dithian; A.-M. Sepulchre, G. Lukacs, G. Vass, and S. D. Gero, Bull. Soc. Chim. Fr., 1972, 4000. The regio-selectivity can be explained in terms of diaxial opening of the oxirane-ring.[4)]

6) T. D. Inch and G. J. Lewis, Carbohydr. Res., 15, 1 (1970).

7) For the reaction of oxiranes with organoalminium reagents, see for example, H. Yamamoto and H. Nozaki, Angew. Chem. Int. Ed., 17, 169 (1978). T. Suzuki, H. Saimoto, H. Tomioka, K. Oshima, and H. Nozaki, Tetrahedron Lett., 23, 3567 (1982).

8) G. N. Richards and L. F. Wiggins, J. Chem. Soc., 1953, 2442. See also ref. 6).

9) For the reaction of oxiranes with Grignard reagents in the presence of copper catalyst, see C. Huynh, F. Derguini-Boumechal, and G. Linstrumelle, Tetrahedron Lett., 1979, 1503.

10) R. U. Lemieux, E. Frage, and K. A. Watanabe, Can. J. Chem., 46, 61 (1968).

(Received November 27, 1982)