Reaction of α-Hydroxydichloromethyl Derivatives with Cesium Acetate

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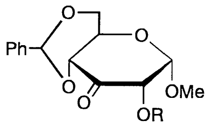
The reactions of methyl 4,6-*O*-benzylidene-2-*O*-benzoyl- and -2-*O*-methyl-*α*-D-*ribo*-hexopyranosid-3-ulose with dichloromethyllithium gave the corresponding *α*-hydroxydichloromethyl derivatives in 75% and 87% yields, respectively. The structures of these products were determined by derivation into known compounds, respectively. A novel reaction of dichloromethyl derivatives with cesium acetate was found to give 3-*α*-hydroxyaldehyde or 3-*α*-acetoxyaldehyde derivative as a main product. S_N2 inversion via spirochloroepoxide was suggested in this reaction by determining configuration of each product.

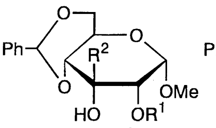
In a previous paper,[1] the authors have reported the usefulness of spirochloroepoxide derivative via *α*-hydroxydichloromethyl derivative for synthesizing functionalized branched-chain sugars. In that work, when dichloromethyl derivatives or the corresponding spirochloroepoxides are treated with nucleophile such as N_3^-, H^-, or Cl^-, which was introduced with complete regiospecificity and S_N2 fashion at the *β*-carbon in respect to the chloro group, to give the corresponding *α*-substituted aldehyde in good yield. On the other hand, the similar reaction was carried out with MeO^- to give an unexpected *α*-hydroxydimethylacetal derivative with displacement reaction at *α*-carbon in good yield. This reaction seems that such kind of HO^- and RO^-, which has high nucleophilicity, react easily with chlorine at *α*-carbon. Further, a similar reaction with sodium acetate gave only an *α*-chloroaldehyde, with chlorine migration, instead of *α*-acetoxyaldehyde. It seems that NaOAc have not sufficient reactivity to react at either *α*-carbon or *β*-carbon in spirochloroepoxide formed intermediary, therefore only migration of chlorine may occur by the conditions used. Then, if we can succeed to introduce AcO^- at *β*-carbon by using more effective reagent such as cesium acetate (CsOAc),[2] it must be more useful synthetic method. Along this line, we examined the reaction of dichloromethyl derivatives with CsOAc. The starting materials were synthesized in the following way. The reactions of methyl 4,6-*O*-benzylidene-2-*O*-methyl- and -2-*O*-benzoyl-*α*-D-*ribo*-hexopyranosid-3-ulose (**1** and **2**)[3,4] with dichloromethyllithium, that was prepared from CH_2Cl_2 and lithium diisopropylamide at -78 °C in oxolane, gave methyl 4,6-*O*-benzylidene-3-*C*-dichloromethyl-2-*O*-methyl-*α*-D-allopyranoside (**3**) and its 2-OH derivative (**4**) in 87% and 75% yields, respectively. A usual benzoylation (benzoyl chloride / pyridine) of **4** gave **5** in 94% yield. Acetyl derivative of **4** was also obtained with Ac_2O / pyridine in quantitative yield. The configurations of **3** and **4** were determined by the following way. Compounds **3** and **4** were treated with Bu_3SnH and AIBN in toluene to afford the corresponding 3-*C*-methyl derivatives (**6** and **7**), respectively, of which physical data were identical with those reported.[3,4]

The reactions of **3**, **4**, and **5**, each of which has a different protecting group at *C*-2, with CsOAc were examined to compare the reactivity. The reaction of **3** with CsOAc (10 equiv.) and 18-crown-6 (2 equiv.) in toluene under reflux gave a syrupy methyl 3-*O*-acetyl-4,6-*O*-benzylidene-3-*C*-formyl-2-*O*-methyl-*α*-D-glucopyranoside (**8**) in 78% yield. In a similar way, the reaction of **4** gave the corresponding 3-*O*-acetyl-2-hydroxy derivative (**9**) in 83% yield, and **5** gave both 2-*O*-benzoyl-3-hydroxy derivative (**10**) and 2-*O*-benzoyl-3-spirochloroepoxide derivative (**11**) in 60% and 12% yields, respectively. The configuration of **8** was supported by NOE (H-5 and CHO, 12%), and **9** was determined by derivation into known methyl 2,3'-di-*O*-acetyl-4,6-*O*-benzylidene-3-*C*-hydroxymethyl-*α*-D-glucopyranoside (**12**),[5] as follows. Compound **9** was treated with excess equiv. of $NaBH_4$ / MeOH at r.t., then acetylated with Ac_2O / pyridine at r.t. to give **12** in 81% yield. It seems that deacetylation reaction of *α*-acetoxyaldehyde occurs easily depending on the substrate. In a similar way, compound **10** gave also the same di-*O*-acetyl derivative **12** in 88% yield. The reactivity of **5** with AcO^- was examined as follows. The reaction of **5** with CsOAc (5 equiv.) and 18-crown-6 (2 equiv.) in toluene at 90 °C gave only **11** in 82% yield, and a similar reaction of **5** with NaOAc (10 equiv.) and 15-crown-5 (2 equiv.) in toluene under reflux gave also only **11** in 90% yield. Further, the reaction of **5** with NaOAc (10 equiv.) and a catalytic amount of 15-crown-5 in HMPA at 70 °C gave the corresponding *α*-chloroaldehyde **13** in 92% yield. The above results show that the reactions of 3-uloses (**1** and **2**) with dichloromethyllithium occur from less hindered side (equatorial attack) to give equatorial dichloromethyl derivatives and the reactions of the dichloromethyl derivatives (**3**, **4**, and **5**) with CsOAc occur with inversion to give the axial formyl derivative (C-C bond is formed in more hindered side) via spirochloroepoxide. Recently, we found also, dichloromethyl derivatives are easily converted into spirochloroepoxide by treatment with base, which have no nucleophilicity (such as DBU) in DMSO.

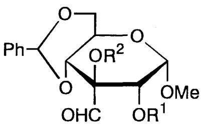
These reactions may useful for preparing both epimeric *α*-hydroxyaldehyde from the same intermediate, dichloromethyl derivative.



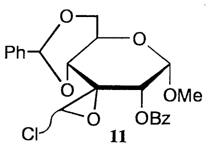
1 R=Me
2 R=Bz



3 R^1=Me, R^2=$CHCl_2$
4 R^1=H, R^2=$CHCl_2$
5 R^1=Bz, R^2=$CHCl_2$
6 R^1=Me, R^2=Me
7 R^1=H, R^2=Me



8 R^1=Me, R^2=Ac
9 R^1=H, R^2=Ac
10 R^1=Bz, R^2=H



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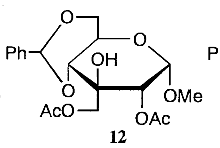

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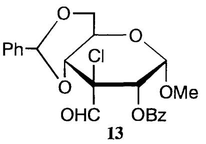

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References and Notes

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