Pergamon

Tetrahedron Letters, Vol. 37, No. 16, pp. 2799-2800, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00432-7

Convenient Synthesis of Both Epimeric α-Hydroxyaldehydes from α-Hydroxydichloromethyl Derivative

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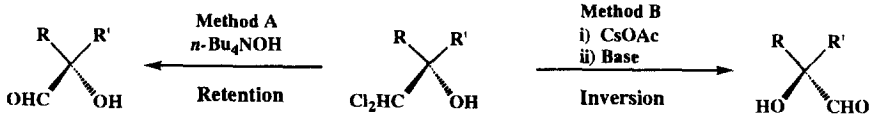
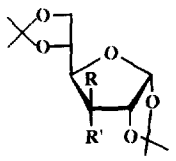
Abstract: The reaction of 3-*C*-dichloromethyl-1,2:5,6-di-*O*-isopropylidene-α-D-*allo*-hexofuranose, methyl 4,6-*O*-benzylidene-3-*C*-dichloromethyl-2-*O*-methyl-α-D-allopyranoside, methyl 2,3-di-*O*-benzyl-4-*C*-dichloromethyl-6-*O*-triphenylmethyl-α-D-galactopyranoside, and methyl 4-*C*-dichloromethyl-2,3-di-*O*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside and -α-D-glucopyranoside with *n*-Bu4NOH or CsOAc gave the epimeric α-hydroxyaldehyde derivatives, respectively.

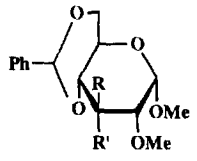
Previously,[1,2] the authors have reported the usefulness of spirochloroepoxide derivatives available from α-hydroxydichloromethyl derivatives in the synthesis of functionalized branched-chain sugars. In these branched-chain sugars, α-hydroxyaldehyde derivatives are considered to be especially useful chiral synthons for natural products synthesis. The reaction of α-hydroxydichloromethyl derivatives with cesium acetate (CsOAc) gave the corresponding α-hydroxyaldehydes with complete regiospecificity and in SN2 fashion at the β-carbon in respect to the chloro group. In this paper, the authors would like to report that the reaction of α-hydroxydichloromethyl derivatives with tetrabutylammonium hydroxide (*n*-Bu4NOH) gives the corresponding α-hydroxyaldehyde derivatives attended by a displacement (OH^-) reaction at the α-carbon, and also the reaction of the same α-hydroxydichloromethyl derivatives with CsOAc gives the epimeric α-hydroxyaldehyde derivatives.

At first, the reaction conditions were examined by using compound (**1**)[1] as follows. The reactions of **1** with NaOH in DMSO, KOH in DMSO, and *n*-Bu4NOH (40% in water, 5.0 equiv.) in toluene under heating conditions gave many spots on TLC, respectively. On the other hand, when the reaction of **1** with *n*-Bu4NOH (40% in water, 5.0 equiv.) was carried out in DMSO at room temperature for a short time (30 sec) and the reaction mixture was poured into saturated aq.NH_4Cl, then extracted with ethyl acetate, the corresponding unstable α-hydroxyaldehyde (**2**) was obtained in 60% yield. The configuration of **2** was supported by derivation into a known hydroxymethyl derivative.[1] The 3-epimer of **2** (**3**) was newly synthesized by the

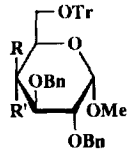




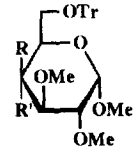
1 R=$CHCl_2$ R'=OH
2 R=CHO R'=OH
3 R=OH R'=CHO



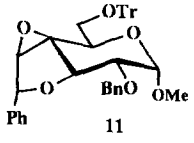
4 R=$CHCl_2$ R'=OH
5 R=CHO R'=OH
6 R=OAc R'=CHO
7 R=OH R'=CHO



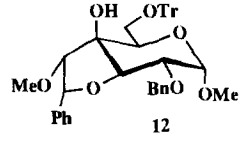
8 R=OH R'=$CHCl_2$
9 R=OH R'=CHO
10 R=CHO R'=OH



13 R=$CHCl_2$ R'=OH
14 R=OH R'=$CHCl_2$
15 R=CHO R=OH
16 R=OH R'=CHO



11



12

reaction of **1** with CsOAc (10.0 equiv.) and 18-crown-6 (7.0 equiv.) in toluene under reflux conditions in 35% yield for direct comparison of their physical data. Compound (**3**) was also too unstable to purify. In a similar manner as above, the reactions of **4**,[2] **8**, **13**, and **14** with *n*-Bu4NOH in DMSO gave **5**, **9**, **15**, and **16** in 80, 30, 73, and 70% yields, respectively. In the reaction of compound (**8**), bicyclic compound (**11**) was also obtained in 63% yield as a side product. The structure of **11** was confirmed by NMR (^1H, ^{13}C, ^{13}C-DEPT, ^1H-^1H COSY, ^{13}C-^1H COSY, and HMBC), elemental analysis, and chemical derivation into **12** by refluxing with NaOMe/MeOH (quantitative yield). Apparently, the reaction mechanism affording compound (**11**) is that the spiroepoxycarbene arising from the spirochloroepoxide reacts with the neighboring benzyl group. The epimers of **5**, **9**, **15**, and **16** (**7**, **10**, **16**, and **15**) were synthesized by using CsOAc as follow. Compound (**7**) was derived in good yield from known compound (**6**)[2] by treating with Et3N/MeOH (ca. pH 9) at room temperature for 30 min. In a similar manner, the reactions of **8** and **14** with CsOAc and 18-crown-6 in toluene followed by treatment with Et3N/MeOH gave **10** and **15** in 85 and 40% yields, respectively. The reaction of **13** with CsOAc (10.0 equiv.) and 18-crown-6 (7.0 equiv.) in toluene under reflux conditions gave only the corresponding spirochloroepoxide in 87% yield, but a similar reaction in DMSO at 100 °C for 6h (this condition was not suitable for other α-hydroxydichloromethyl derivatives) gave **16** in 70% yield. It was noteworthy that the reaction of α-hydroxydichloromethyl derivatives with CsOAc gave the corresponding α-hydroxyaldehydes or α-acetoxyaldehydes depending upon the substrates. This type of acetyl group seems to be easily cleaved by a weak base. The configurations of the α-hydroxyaldehydes were supported by NOE and direct comparisons of the physical constants of both epimers, respectively.

As mentioned above, these results may provide the answer regarding the stereochemical course of Köbrich's work[3] (OH^- reacts at the α-carbon or β-carbon in respect to the chloro group), which did not discuss the configurations of the products. In conclusion, two modes of reactions of α-hydroxydichloromethyl derivatives either with *n*-Bu4NOH or with CsOAc may promise a convenient method for the selective preparation of both epimeric α-hydroxyaldehyde derivatives.

References and Notes

1. K. Sato, K. Suzuki, M. Ueda, M. Katayama, and Y. Kajihara, *Chem. Lett.*, **1991**, 1469-1472.
2. K. Sato, K. Suzuki, and Y. Hashimoto, *Chem. Lett.*, **1995**, 83.
3. G. Köbrich and W. Werner, *Tetrahedron Lett.*, **1969**, 2181-2183.

(*Received in Japan* 18 *January* 1996; *revised* 22 *February* 1996; *accepted* 29 *February* 1996)