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Novel methods for synthesizing 2-chloroaldehyde from carbonyl compounds and converting it into 2-hydroxyaldehyde derivatives

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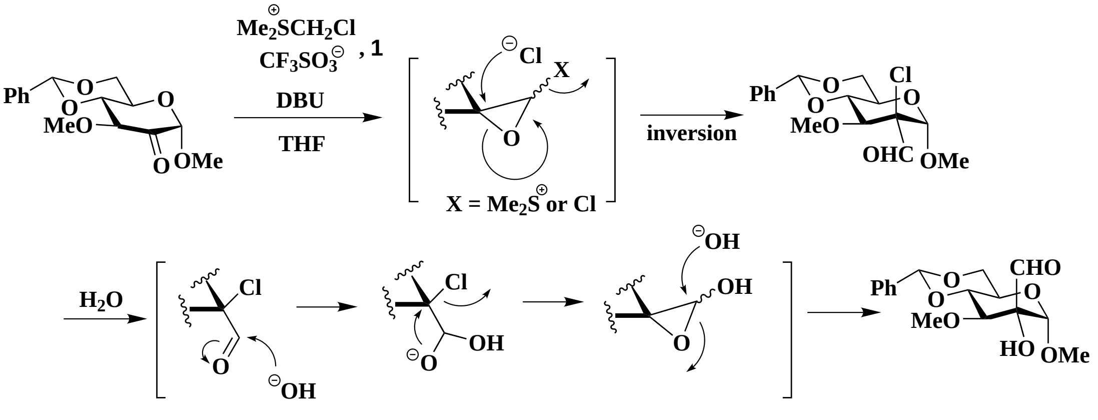
Abstract—2-Chloroaldehyde derivatives were synthesized from carbonyl compounds with [chloromethyl (dimethyl)sulfonium trifluoromethanesulfonate, (**1**)] and DBU in THF in good yields. Further, 2-chloroaldehyde derivatives were converted into the corresponding 2-hydroxyaldehydes by treating the derivatives with n-Bu$_4$NOH in good yields with the inverted configuration. The stereochemistry of all the products were determined by NMR (NOE). © 2001 Elsevier Science Ltd. All rights reserved.

In the previous papers,[1] K. Sato, one of the three authors of this report, has described a facile and effective reagent, dichloromethyllithium, for synthesizing various functionalized branched-chain sugars via 2,2-dichloroethanol and 2-chloro-oxyrane derivatives. In addition, both 2-chloroaldehyde and 2-hydroxyaldehyde,[2] derived from the above intermediates, are themselves useful precursors for synthesizing functionalized branched-chain compounds. To facilitate progress in this area, convenient methods for synthesizing 2-chloro-oxyrane, 2-chloroaldehyde and 2-hydroxyaldehyde derivatives from carbonyl compounds are required. In 1997, Kaczmarczyk et al.[3] described a reagent [chloromethyl(dimethyl)sulfonium trifluoromethanesulfonate, (**1**)] that can be used for preparing dimethylacetals of 2-hydroxyaldehydes from ketones under basic conditions. In the paper, they reported that the corresponding 2-chloro- or 2-dimethylsulfonium-oxyranes are presumably transient intermediates.[4] Therefore, we tried to isolate the 2-substituted-oxyranes by using this reagent **1** in a similar manner as that used for obtaining unsubstituted-oxyranes from ketones and either dimethyloxosulfonium methylide or dimethylsulfonium methylide.[5] The reactions of carbonyl-sugars (uloses) with **1** were carried out using 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in tetrahydrofuran (THF), instead of the reported sodium methoxide in methanol, to provide 2-chloroaldehydes as the unexpected prod-



Scheme 1.

Keywords: carbonyl compounds; sulfonium salts; carbohydrates; ylides.

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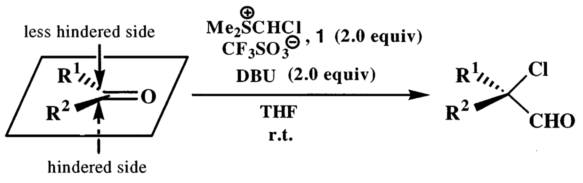
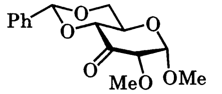
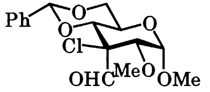
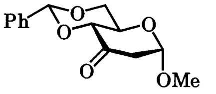
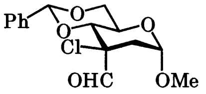
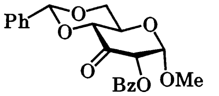
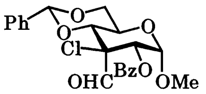
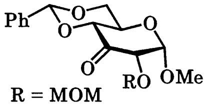
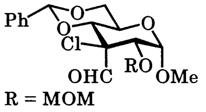
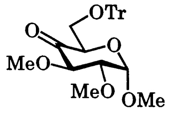
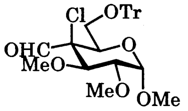
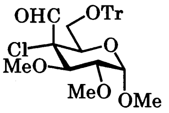
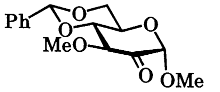
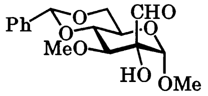
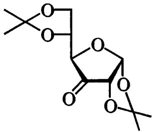
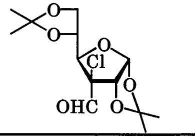
ucts, in good yields. Despite our repeated trials, 2-substituted-oxyranes could not be isolated. In this reaction, 2-chloroaldehydes are presumably produced via reactive 2-substituted-oxyrane transient intermediates[6] and the reported dimethylacetals of 2-hydroxyaldehydes may also be produced via these 2-chloroaldehydes.[7] Presented with these results, we tried to convert 2-chloroaldehyde into 2-hydroxyaldehyde by treating 2-chloroaldehyde with tetrabutylammonium hydroxide in toluene. This reaction was successful and constituted a new synthetic procedure for synthesizing 2-hydroxyaldehydes in good yields. This paper describes the results of a series of reactions and the associated stereochemistry.

Synthesis of 2-chloroaldehydes from uloses

We used the conformationally rigid carbohydrate compounds to reveal the stereochemistry in this work. Run 1 was carried out as follows: A mixture of methyl 4,6-*O*-benzylidene-2-*O*-methyl-α-D-*ribo*-hexopyranosid-3-ulose (50 mg, 0.17 mmol), **1** (88 mg, 0.34 mmol), and DBU (0.05 mL, 0.34 mmol) in THF (2.0 mL) was stirred at rt for 5 min under argon. The reaction mixture was poured into satd aq. NH_4Cl and extracted with $CHCl_3$. The extract was washed with brine and water, dried over anhydrous magnesium sulfate, and evaporated to furnish a residue. Purification of the residue on a column of silica gel (hexane/ethyl acetate 1:1) gave 2-chloroaldehyde in quantitative yield. The structure of 2-chloroaldehyde was confirmed by comparing the physical constants with those of the known compound, which was prepared by a previously published method,[1] 500 MHz ^1H NMR (NOE), elemental analysis, and Beilstein's test. By analogous procedures, each carbonyl compound in Table 1 provided the corresponding 2-chloroaldehyde derivative in good yield, except Run 6. When using 2-ulose

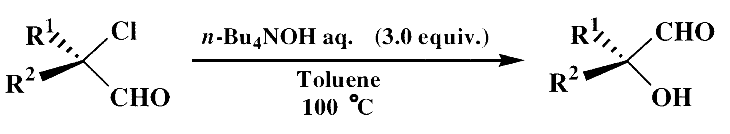
Table 1. Synthesis of 2-chloroaldehydes from uloses

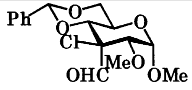
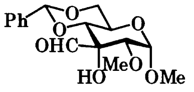
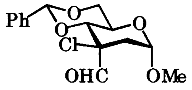
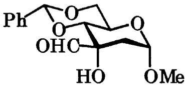
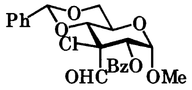
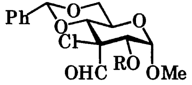
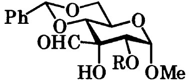
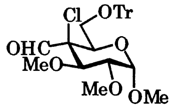
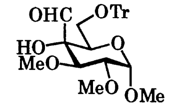
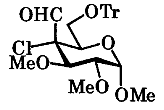
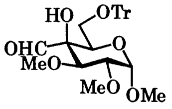
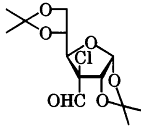
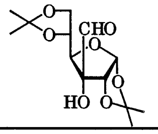


Run	Ulose	α-Chloroaldehyde	
1			y. quant.
2			y. 86%[a)]
3			y. 70%
4			y. quant.
5			y. 39%
			y. 40%
6			y. 98%
7			y. 75%

a) In this case, **1** was used with 3.0 equivalent.

Table 2. Conversion of 2-chloroaldehydes into 2-hydroxyaldehydes



Run	2-Chloroaldehyde	2-Hydroxyaldehyde
8		 y. quant.
9		 y. 89%
10		many spots on TLC
11	 R = MOM	 R = MOM y. 93%
12		 y. 93%
13		 y. 92%
14		 y. 86%

(Run 6), the reactive product (2-chloroaldehyde) apparently reacts further with OH$^-$ during the post-treatment with water to produce 2-hydroxyaldehyde via 2-hydroxyoxyrane, as shown in Scheme 1. NOE data for the assignment of the configuration of these products are summarized in Ref. 8. The stereoselectivities in the reaction of uloses with **1** are controlled in the same manner as other general nucleophiles described in the previous paper.[9]

Conversion of 2-chloroaldehydes into 2-hydroxyaldehydes

Run 8 was carried out as follows: To a solution of the 2-chloroaldehyde derivative of methyl 4,6-*O*-benzylidene-2-*O*-methyl-α-D-*ribo*-hexopyranosid-3-ulose (50 mg, 0.15 mmol) in toluene (3.0 mL), *n*-Bu$_4$NOH aq. (40 wt%, 0.1 mL, 0.45 mmol) was added and the reaction mixture was kept at 100°C for 5 min. The reaction mixture was poured into satd aq. NH$_4$Cl, extracted with CHCl$_3$ and washed with water. The extract was evaporated to give a residue, which was purified on a column of silica gel (hexane/ethyl acetate 1:2). The desired 2-hydroxyaldehyde was obtained in quantitative yield. The structure was confirmed by comparing the physical constants with those of the known compound, which was prepared by our previously published method with reference to **1**, 500 MHz ^{1}H NMR (NOE), and elemental analysis. By analogous procedures, each 2-chloroaldehyde derivative in Table 2 provided the corresponding 2-hydroxyaldehyde derivative in good yield, except Run 10. It appears that this reaction also proceeds by the mechanism given in Scheme 1. In the case of Run 10, many products are produced, most likely due to the participation of the de-benzoylated 2-hydroxyl group. NOE data for the assignment of the configuration of these products are summarized in Ref. 10.

In conclusion, we have developed a new and efficient procedure for preparing 2-chloroaldehydes and converting them into 2-hydroxyaldehydes, which may be readily employed for large-scale synthesis.

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8. NOE data for the products of Runs 1–7. Run 1: (CHO–H-5, 10.2%), Run 2: (CHO–H-5, 8.0%), Run 3: (CHO–H-5, 9.8%), Run 4: (CHO–H-5, 9.6%), Run 5: (axial CHO–H-2, 8.0%); (equatorial CHO–H-3, 7.1%), Run 6: (CHO–H-4, 7.8%), Run 7: the physical data of the product was identical with that reported.[1a]
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10. NOE data for the products of Runs 8–14. Run 8: (OH–H-5, 7.3%), Run 9: its 3-*C* epimer derived from dichloromethyl derivative[1] (CHO–H-5, 13.0%), Run 11: (OH–H-5, 6.7%), Run 12: (CHO–H-2, 8.0%), Run 13: (CHO–H-3, 6.0%; CHO–H-5, 4.3%), Run 14: the physical data of this product was identical with that reported.[1a]