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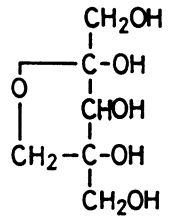
SELECTIVE SYNTHESIS OF DL-DENDROKETOSE FROM FORMALDEHYDE

Toshihiko MATSUMOTO, Masahiro YAMANE, and Shohei INOUE*
Department of Synthetic Chemistry, Faculty of Engineering,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

A one-pot selective formation of a hexulose, dendroketose, was achieved by the addition of an aqueous alkaline solution to the reaction mixture obtained by the condensation reaction of formaldehyde catalyzed by a thiazolium salt.

Since elemental composition of formaldehyde, CH_2O, is the same as that of carbohydrates such as D-glucose, it is considered possible to synthesize carbohydrates by the self-condensation of formaldehyde with carbon-carbon bond formation. This attempt has been made for a long time,[1] and the reaction is called "Formose reaction." Formose reaction is of much interest in connection with the possible importance in a large scale manufacture of edible carbohydrates from a simple material by a facile procedure. However, the reaction catalyzed by calcium hydroxide, a well-known catalyst, gives a complex mixture of about thirty products, making it so difficult to isolate and identify each product. The examples of selective formose reaction which yields specific product have been very limited,[2] although it is strongly desirable to develop the method to obtain a specific product in high yield and with high selectivity.

In our recent studies on the reaction catalyzed by a thiazolium salt in the presence of a base,[3] it was found that dihydroxyacetone (triose) was obtained selectively in high yield. Since dihydroxyacetone is known to give a branched hexulose, DL-dendroketose (1), in the presence of alkali under appropriate conditions,[4,5] the above finding prompted us to examine the possibility of one-pot synthesis of the hexulose from formaldehyde. In the present report is described the first example of the selective formation of DL-dendroketose, by adding an aqueous alkaline solution to the reaction mixture prepared by the condensation of formaldehyde catalyzed by a thiazolium salt.



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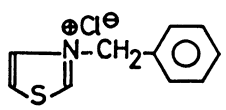
In a 50 cm^3 flask were placed paraformaldehyde (1.5 g, 50 mmol as HCHO), 3-benzylthiazolium chloride (2)[6] (1.106 g, 0.5 mmol), dioxane (10 cm^3), and triethylamine (0.07 cm^3, 0.5 mmol). Dry nitrogen was bubbled into the mixture and then the flask was tightly closed with a glass stopper. The reaction was started by immersing the flask stirred magnetically in an oil bath adjusted to 100 °C. After 30 min



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the resulting solution was cooled by solid CO_2-ethanol bath to room temperature (Step I). To the resulting mixture was added an aqueous alkaline solution (30 cm^3), or water (30 cm^3) containing anion exchange resin (OH^- type), and then the mixture was allowed to stand at room temperature for a prescribed time in nitrogen (Step II).

In Step I and Step II, the consumption of formaldehyde, as determined colorimetrically with chromotropic acid,[7] was 96 and 100%, respectively. An aliquot (0.5 cm^3) of the reaction mixture obtained in Step I was reacted with hydroxylamine hydrochloride (0.1 g) in pyridine (8 cm^3) at 70 °C for 1 h, followed by trimethylsilylation by adding a mixture (2 cm^3) of hexamethyldisilazane and trimethylchlorosilane (2:1 in volume).[8] An aliquot (5 cm^3) of the reaction mixture obtained in Step II was neutralized with 1 mol dm^{-3} hydrochloric acid, and the solution was evaporated to dryness to give a syrupy product. The syrup was converted into the trimethylsilylated (TMS) oxime derivative by the procedure as described above.

Figure 1 (a) shows an example of the gas-liquid chromatogram of the TMS-oxime derivative of the product in Step I. The main product corresponding to peak 1 was confirmed to be dihydroxyacetone as described in the previous paper.[3] From the area of peak 1, the amount of dihydroxyacetone formed in Step I was estimated 91 wt-% of the reacted formaldehyde. Figure 1 (b) shows the gas-liquid chromatogram of the TMS-oxime derivative of the product in Step II prepared by reacting the formaldehyde condensation mixture (Step I; corresponding to Fig. 1 (a)) with 0.5 mol dm^{-3} aqueous sodium hydroxide solution at room temperature for 0.5 h. From the chromatogram it can be seen that the products corresponding to two peaks (peak 2) were formed selectively. Since TMS-oxime derivative of an unsymmetrical carbonyl compound gives two peaks corresponding to the syn and anti oximes in the gas-liquid chromatogram,[8] the main peaks (peak 2) are considered to correspond to a single compound. Indeed, the compound corresponding to peak 2 was isolated from the reaction mixture of Step II as the benzoylisopropylidene derivative,[9] which was confirmed to be O-benzoyl-di-O-isopropylidene-DL-dendroketose. The ^1H NMR, ^{13}C NMR, and IR spectra of the isolated benzoylisopropylidene derivative and the retention time of the TMS-oxime derivative (peak 2 in Fig. 1 (b)) were in agreement with those of the respective derivatives of the authentic sample of DL-dendroketose prepared according to

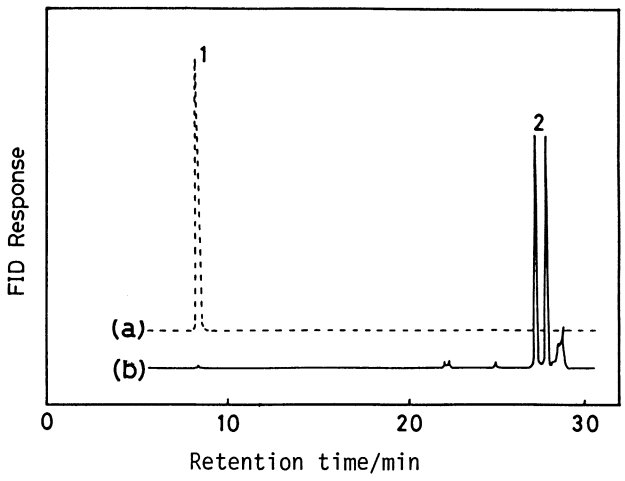

Fig. 1. Gas-liquid chromatogram of the trimethylsilylated oxime derivatives of the products obtained by the reactions: (a) Paraformaldehyde (50 mmol as HCHO), 3-benzylthiazolium chloride (0.5 mmol), triethylamine (0.5 mmol), dioxane (10 cm^3), 100 °C, 0.5 h (Step I); (b) addition of 0.5 mol dm^{-3} aqueous NaOH solution (30 cm^3) to the reaction mixture obtained in Step I, room temperature, 0.5 h (Step II).

Table 1. Synthesis of DL-dendroketose (1) from formaldehyde[a)]

Run	Base in Step II	Reaction time of Step II / h	Yield of DL-dendroketose[c)] / %
1	0.5 mol dm^{-3} NaOH	0.5	74
2	0.5 mol dm^{-3} NaOH	2.5	63
3	0.5 mol dm^{-3} NaOH	5	55
4	0.1 mol dm^{-3} NaOH	4	63
5	0.25 mol dm^{-3} Na_2CO_3	4	53
6	0.5 mol dm^{-3} Quinuclidine	5	27
7	Amberlite IRA-402(OH^-)[b)]	4	51
8	Amberlyst A-27(OH^-)[b)]	4	8

a) Step I; paraformaldehyde (50 mmol as HCHO), 3-benzylthiazolium chloride (0.5 mmol), triethylamine (0.5 mmol), dioxane (10 cm^3), 100 °C, 0.5 h. Step II; addition of a base in water (30 cm^3) to the reaction mixture obtained in Step I, room temperature.
b) 3 mg equivalent of OH^- in water (30 cm^3).
c) Based on the starting formaldehyde by gas-liquid chromatography of the trimethylsilylated oxime derivatives.

the method of Utkin.[4)] Therefore, the main product in Step II corresponding to peak 2 in the gas-liquid chromatogram is DL-dendroketose, a branched hexulose.

Table 1 shows the yield of DL-dendroketose under various conditions in Step II. The yield was evaluated by the ratio of the amount of DL-dendroketose to that of starting formaldehyde based on the gas-liquid chromatographic measurements of the TMS-oxime derivative using D-fructose as an internal standard. In the reaction with 0.5 mol dm^{-3} aqueous sodium hydroxide solution for 0.5 h (run 1), the yield of DL-dendroketose was as high as 74%, indicating that 85% of dihydroxyacetone formed in Step I was converted into DL-dendroketose in Step II. A wide variety of bases such as inorganic base, organic base, and ion exchange resin gave satisfactory yield of DL-dendroketose.

Similar results were obtained when 3-ethylthiazolium bromide or 3-benzylthiazolium bromide was employed as catalyst in Step I, and when dimethyl sulfoxide or N,N-dimethylformamide was used as solvent in Step I.

References

1) A. Butlerow, Ann. Chem., 120, 295 (1861).
2) Y. Shigemasa, O. Nagae, C. Sakazawa, R. Nakashima, and T. Matsuura, J. Am. Chem. Soc., 100, 1309 (1978); T. Matsumoto, M. Komiyama, and S. Inoue, Chem. Lett., 1980, 839; Y. Shigemasa, S. Akagi, and R. Nakashima, Carbohydr. Res., 80, C1 (1980); Y. Shigemasa, T. Hamada, M. Hirabayashi, E. Waki, R. Nakashima, K. Harada, and M. Suzuki, Chem. Lett., 1981, 899; T. Matsumoto, and S. Inoue, J. Chem. Soc., Perkin Trans. 1, 1982, 1975.
3) T. Matsumoto and S. Inoue, J. Chem. Soc., Chem. Commun., 1983, 171; T.

Matsumoto, H. Yamamoto, and S. Inoue, J. Am. Chem. Soc., in press.

4) L. M. Utkin, Dokl. Akad. Nauk. SSSR, 67, 301 (1949); Chem. Abstr., 44, 3910 (1950).

5) C. D. Gutsche, D. Redmore, R. S. Buriks, K. Nowotny, H. Grancer and C. W. Armbruster, J. Am. Chem. Soc., 89, 1235 (1967).

6) 3-Benzylthiazolium chloride was prepared by heating thiazole with benzyl chloride: Mp 154-155 °C (ethanol-ether); ^{1}H NMR (CD_3OD) δ 5.66 (2H, s, $-CH_2-Ph$), 7.08-7.42 (5H, m, benzene ring), 8.10 (1H, m, C-5 proton of thiazolium ring), 8.27 (1H, m, C-4 proton), and 10.06 (1H, s, C-2 proton). Satisfactory analytical results were obtained for this compound.

7) I. Yamashina, T. Yamakawa, and S. Suzuki, "Experimental Methods in Biochemistry," ed by the Japanese Biochemical Society, Tokyo Kagaku Dozin, Tokyo (1979), Vol. 4, p. 478.

8) D. Anderle, J. Königstein, and V. Kováčik, Anal. Chem., 49, 137 (1977).

9) The benzoylisopropylidene derivative was prepared by the reaction between the syrupy product obtained in Step II and acetone in the presence of a small amount of sulfuric acid,[10] followed by the reaction of the resulting isopropylidene derivative with benzoyl chloride in pyridine.[11] Two recrystallizations from ethanol gave white crystals (10%): Mp 123-124 °C (ethanol) (lit,[4] 121 °C); IR (KBr) 1720, 1600, 1585, and 1280 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35, 1.41, 1.45, and 1.46 (3H, s, $-CH_3$, respectively), 4.03, 4.09, 4.12, 4.29, 4.31, 4.45, 4.48, 4.50, 4.63, and 4.66 (7H (sum of 10 peaks), s, backbone protons (CH, CH_2)), 7.44 (2H, m, m-position of benzene ring), 7.58 (1H, m, p-position), and 8.10 (2H, m, o-position); ^{13}C NMR ($CDCl_3$) δ 26.4 (q), 27.4 (q), 65.2 (t), 69.3 (t), 73.6 (t), 87.1 (d), 90.2 (s), 111.7 (s), 113.0 (s), 113.9 (s), 128.3 (d), 129.8 (d), 129.8 (s), 133.2 (d), and 166.1 (s). Found: C, 62.56; H, 6.74%. Calcd for $C_{19}H_{24}O_7$: C, 62.62; H, 6.64%.

10) O. T. Schmidt, "Methods in Carbohydrate Chemistry," ed by R. L. Whistler, M. L. Wolform, and J. N. BeMiller, Academic Press Inc., New York (1963), Vol. 2, p. 318.

11) H. G. Fletcher Jr., "Methods in Carbohydrate Chemistry," ed by R. L. Whistler, M. L. Wolform, and J. N. BeMiller, Academic Press Inc., New York (1963), Vol. 2, p. 231.

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