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Aldol Type Reaction of Unprotected Sugars in Methanol

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Abstract: Although aldol condensation of 1,3-dihydroxyacetone with formaldehyde in methanol catalyzed by CaCl₂/KOH gave glycero-tetrulose, the reaction catalyzed by Ca(OH)₂ preferentially gave 1,3-dihydroxyacetone dimer. The result was explained by the formation of a chelated enolate. This sequence was successfully applied to the stereoselective synthesis of *threo*-3-pentulose.

Selective transformation of unprotected saccharides has received some attention in connection with simplification of protection-deprotection strategy of the hydroxyl groups.^{1,2} Aldol reaction of unprotected sugars has been of interest from synthetic and chemical evolutional viewpoints.^{3,4} Difficulty in stereochemical control and competition with retro-aldol and isomerization reactions have been the main obstacle in this type of reaction.⁵ We have investigated aldol reaction of sugar under primitive conditions in which unprotected sugars, metal hydroxides, water or alcohols, and formaldehyde were employed.⁴ Reported herein are preferential formation of dendroketose (4) or *glycero*-tetrulose (2) from 1,3-dihydroxyacetone (1) and stereoselective synthesis of *threo*-3-pentulose (3) from 2 by the aldol type reaction in methanol.

As shown in Table 1 (Run 1), treatment of 1 and formaldehyde in methanol with $Ca(OH)_2$ selectively gave dihydroxyacetone dimer 4⁶ (Path A). In contrast, the reaction catalyzed by CaCl₂/KOH (Run 4) mainly gave one- and two-carbon extension products, 2 and 3⁴ (Path B).⁷

These results were rationalized by the concentration of dissolved calcium ion. In comparison with Ca(OH)₂, CaCl₂/KOH system provides much more soluble calcium cation. Therefore, a strained (E)-enolate **6** might be stabilized by the coordination of C1- and C3-hydroxyl groups to the second calcium cation.⁴ The smallest carbonyl compound, formaldehyde, approaches to this enolate **6** to give **4**, but relatively bulky **1** is suppressed to react with **6**. This hypothesis was confirmed by the experiments shown in Runs 3, 4, and 5. Compared with the proportion of Path A leading to the dimer **4**, that of Path B



Run	Ketose <u>HCH</u>		<u>) Reagent</u>	Time	Conversion	Yield/%				Selectivity ^{b)}
		mol/l	mol/l	_ h _	%	2	3	7	4	Path B/Path A
1	1	0.06	Ca(OH) ₂ 0.1	0.5	45	1	1		59	6/94
2	1	1.0	Ca(OH) ₂ 0.1	0.17	60	19	3		43	51/49
3	1	1.0	CaCl ₂ /KOH 0.01/0.01	0.33	51	30	6		53	58/42
4	1	1.0	CaCl ₂ /KOH 0.1/0.01	0.67	52	44	16		36	77 / 23
5	1	1.0	CaCl ₂ /KOH 1.0/0.01	0.83	47	36	35		16	90/10
6	2	1.2	CaCl ₂ /KOH 0.1/0.01	1.5	53		65c)	5		
7	2	3.0	SmCl ₃ /KOH 0.1/0.01	36	57		88d)	3		

Table 1. Aldol Type Reaction of Unprotected Ketoses and Formaldehydea)

a) Substrate, 0.03 mol/l; methanol, 50 ml; 0 °C; yield, based on the consumed substrate.

b) Path B / Path A \approx [(yield of 2) + (yield of 3)] / [(yield of 4)/2].

c) Threo: erythro = 90: 10. d) Threo: erythro = 97: 3.

leading to 2 and 3 increased with increasing the amount of added $CaCl_2$ which provided calcium cation necessary to form 6. When less soluble $Ca(OH)_2$ was employed, not only 6 but also a sterically less strained (Z)-enolate 5 might be formed. Because electron withdrawing CH₂OH groups activated the carbonyl group in 1, second dihydroxyacetone molecule instead of formaldehyde coordinated to the metal cation in 5 to give the dimer 4 (Run 1). Even in the presence of 33 fold-molar excess of formaldehyde relative to 1 in Run 2, the proportion of Path A was nearly same as that of Path B.

This sequence was successfully applied to the reaction of the enolate of 2 with formaldehyde to afford 3 in Run 6, and a regioisomer, 3-C-(hydroxymethyl)tetrulose (7), was produced a little. High *threo* selectivity in the synthesis of 3 is attributed to the formation of a chelated enolate⁴ like 6. Finally, combination of SmCl₃ with KOH performed this transformation with the higher *threo* selectivity (Run 7).⁸



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- 7. Experimental conditions were mentioned in Table 1 and yields were estimated by gas chromatography as reported in ref. 4.
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