ALDEHYDE ENOLATE. CROSS ALDOL REACTION via TIN(II) ENOLATE

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Tin(II) enolate, formed in situ by the oxidative addition of metallic tin to 2-bromo-2-methylpropanal, reacts with aldehydes to give β -hydroxy aldehydes in fairly good yields.

The employment of the enolates derived from aldehydes in the synthetic reactions is rather difficult because of their easiness to be subjected to aldol condensation. To overcome this difficulty, aldehydes are gerenally converted to the more manageable compounds such as imines, $^{(1)}$ hydrazones, $^{(2)}$ etc. The direct generation of aldehyde enolates from free aldehydes is only achieved by A. van der Gen et al. using potassium hydride.³⁾ It was only applied to the alkylation, however, no successful example of cross aldol reaction between two aldehydes was reported so far.

The cross aldol reaction between two aldehydes is much more difficult because of the following three reasons; 1) the self condensation reaction mentioned above; 2) a further attack of the enolate to the produced β -hydroxy aldehydes to form the higher analogs of the aldol; 3) β -hydroxy aldehydes having α -hydrogen are easily dehydrated to form α,β -unsaturated aldehydes.

Now, we wish to report an example of cross aldol reaction of tin(II) enolate (4), generated from 2-bromo-2-methylpropanal (1) by the oxidative addition of metallic tin as shown in the following Scheme 1.



The followings are assumed; 1) an enolate will be prepared cleanly if the rate of the oxidative addition of metallic tin to α -bromo aldehyde (1) is much faster than that of self condensation reaction of aldehyde (1);⁴⁾ 2) for the steric reason, it is hard for the produced β -stannoxy aldehydes to be subjected to a further attack of the enolate. Moreover, the produced β -hydroxy aldehydes are able to be isolated easily, because they have no α -hydrogen to be dehydrated.

Based on these considerations, the conditions of the reaction were investigated by employing benzaldehyde as a model, and it was found that the followings were required to obtain the desired β -hydroxy aldehydes (<u>6</u>) in good yields; 1) the use of tetrahydrofuran (THF) as the solvent; 2) the preparation of activated metallic tin by the reduction of stannous chloride (<u>2</u>) with metallic potassium (<u>3</u>); 3) the slow addition of α -bromo aldehyde (<u>1</u>) to the suspension of metallic tin and aldehyde (<u>5</u>) to avoid self condensation reaction of α -bromo aldehyde (<u>1</u>); 4) stirring overnight at 0 °C. Based on these experimental conditions, synthesis of β -hydroxy aldehydes (<u>6</u>) was carried out as shown in Table 1.

Table 1. The synthesis of β -hydroxy aldehydes.^{a)}

Aldehyde (5)	Yield of <u>6</u> / %
PhCHO	64
<i>p</i> -С1С ₆ Н ₄ СНО	71
$p-BrC_6H_4CHO$	70
$n - C_{11}H_{23}CHO$	65
$PhCH_2O(CH_2)_3CHO$	74

a) All the products gave satisfactory ¹H-NMR and IR spectra. A typical procedure is described for the synthesis of 3-hydroxy-2,2-dimethyl-3-phenylpropanal: Under an argon atmosphere, anhydrous stannous chloride (379 mg, 2 mmol)⁵⁾ and metallic potassium (78 mg, 2 mmol) were suspended in THF (2 ml), and the suspension was refluxed for 1 h. to form dark gray metallic tin. After the suspension was cooled to 0 °C, a THF (1 ml) solution of benzaldehyde (53 mg, 0.5 mmol) was added. Then a THF (1 ml) solution of 2-bromo-2-methylpropanal (113 mg, 0.75 mmol) was added dropwise, and the reaction mixture was stirred over-

night at 0 °C. The phosphate buffer was added, and the precipitates were removed by filtration. The organic materials were extracted with ethyl acetate, and the combined extracts were washed with brine, and dried over MgSO₄. The solvents were removed under reduced pressure. 3-Hydroxy-2,2-dimethyl-3-phenylpropanal (57 mg, 64%) was isolated by thin layer chromatography on silica gel. ¹H-NMR (CDCl₃) δ 0.73 (3 H, s), 0.80 (3 H, s), 2.73 (1 H, s), 4.70 (1 H, s), 7.13 (5 H, s), 9.47 (1 H, s). IR (NaCl) 3430, 1720 cm⁻¹.

Thus, β -hydroxy aldehydes (6) are obtained in fairly good yields from several aldehydes and α -bromo aldehyde (1) via tin(I) enolate.

References

- 1) G. Stork and S. R. Dowd, J. Am. Chem. Soc., 85, 2178 (1963).
- 2) E. J. Corey and D. Enders, Tetrahedron Lett., 1976, 3.
- P. Groenewegen, H. Kallenberg, and A. van der Gen, Tetrahedron Lett., <u>1978</u>, 491.
- We have already reported on the generation of the enediolate from α-keto aldehyde based on the same assumption. See; T. Mukaiyama, J. Kato, and M. Yamaguchi, Chem. Lett., 1982, 1291.
- 5) It is presumed that the excess stannous chloride plays an important part in the reduction of α -bromo aldehyde (1). Also is the case in Ref. 4.

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