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 re-
actions 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.

Scheme 1.
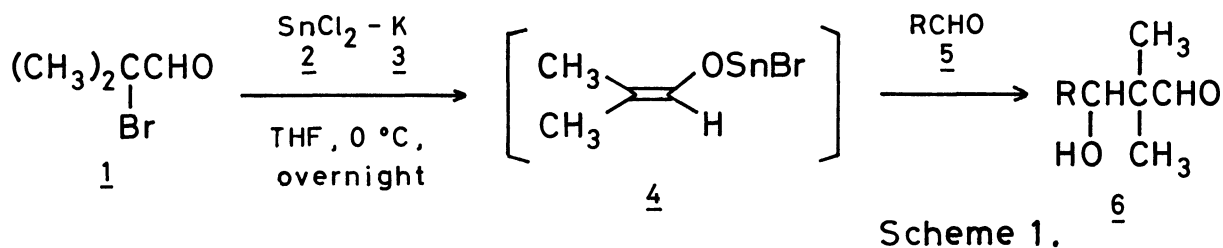
The followings are assumed; 1) an enolate will be prepared cleanly if the
rate of the oxidative addition of metallic tin to α-bromo aldehyde (1) is much
faster than that of self condensation reaction of aldehyde (1);[4] 2) for the
steric reason, it is hard for the produced β-stannoxy aldehydes to be 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 investi-
gated by employing benzaldehyde as a model, and it was found that the followings

were required to obtain the desired β-hydroxy aldehydes (6) 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 (2) with metallic potassium (3); 3) the slow addition of α-bromo aldehyde (1) to the suspension of metallic tin and aldehyde (5) to avoid self condensation reaction of α-bromo aldehyde (1); 4) stirring overnight at 0 °C. Based on these experimental conditions, synthesis of β-hydroxy aldehydes (6) was carried out as shown in Table 1.

Table 1. The synthesis of
β-hydroxy aldehydes.[a]

Aldehyde (5)	Yield of 6 / %
PhCHO	64
p-ClC$_6$H$_4$CHO	71
p-BrC$_6$H$_4$CHO	70
n-C$_{11}$H$_{23}$CHO	65
PhCH$_2$O(CH$_2$)$_3$CHO	74

a) All the products gave satisfactory
   ^{1}H-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 overnight 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 MgSO$_4$. 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. ^{1}H-NMR (CDCl$_3$) 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(II) 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.
   3) P. Groenewegen, H. Kallenberg, and A. van der Gen, Tetrahedron Lett., 1978, 491.
   4) 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.