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A NOVEL METHOD FOR THE SYNTHESIS OF α,β-DIHYDROXY KETONES *via* TIN(II) ENEDIOLATES

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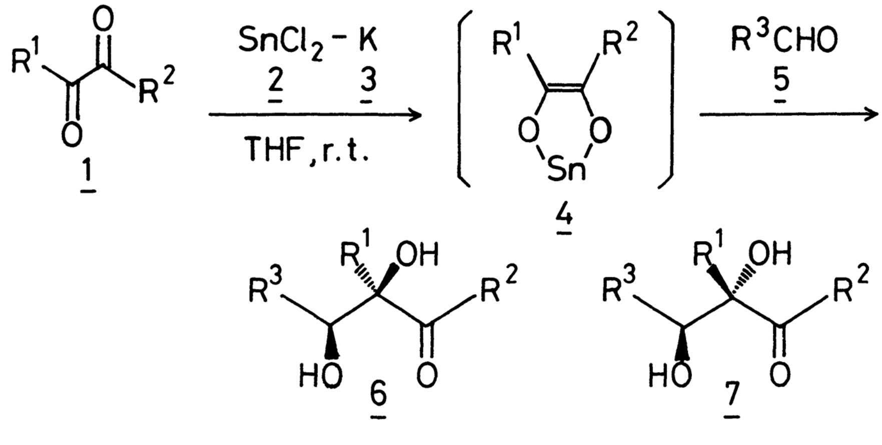
Activated metallic tin, prepared from stannous chloride and metallic potassium, reacts readily with α-dicarbonyl compounds to form tin(II) enediolates, which in turn react with aldehydes under a mild reaction condition to give α,β-dihydroxy ketones in good yields. The reaction proceeds stereoselectively in the presence of hexafluorobenzene.

During our continuous investigations on the exploration of new synthetic reactions by using low valent tin compounds, metallic tin turned out to be a useful reducing agent. Thus, the organotin compounds, formed in situ by the oxidative addition of metallic tin to the organic compounds such as allyl bromide, α-bromo ketones and α-bromo esters, react with carbonyl compounds to yield the corresponding homoallyl alcohols,1) β-hydroxy ketones2) and β-hydroxy esters3) in good yields, respectively.

We now wish to report a convenient method for the synthesis of α,β-dihydroxy ketones (6,7) from α-dicarbonyl compounds (1) and aldehydes (5) in the presence of activated metallic tin, prepared from stannous chloride (2) and metallic potassium (3).

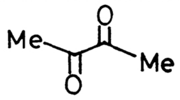
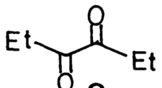
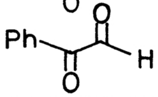
In the first place, the conditions of the reaction were investigated by employing a combination of 3-phenylpropanal and 2,3-butanedione as a model, and it was found that the followings were required to obtain α,β-dihydroxy ketones (6,7) in good yields; 1) the use of tetrahydrofuran (THF) as the solvent; 2) the reduction of stannous chloride (2) with metallic potassium (3); 3) the slow addition of α-dicarbonyl compounds (1) to the suspension of metallic tin and aldehydes (5) to keep away from self-aldol reaction of α-dicarbonyl compounds (1). Based on these preliminary experiments, syntheses of various α,β-dihydroxy ketones (6,7) from the corresponding α-dicarbonyl compounds (1) and aldehydes (5) were carried out under mild reaction conditions as shown in the Scheme I and Table I.

A typical procedure is described for the synthesis of 3,4-dihydroxy-3-methyl-6-phenyl-2-hexanone: Under an argon atmosphere, anhydrous stannous chloride (379 mg, 2 mmol) and metallic potassium (78 mg, 2 mmol) were suspended in THF (2 ml), and the suspension was refluxed for 1hr to form a dark gray metallic tin. After the suspension was cooled to room temperature, a THF (1 ml) solution of



Scheme I

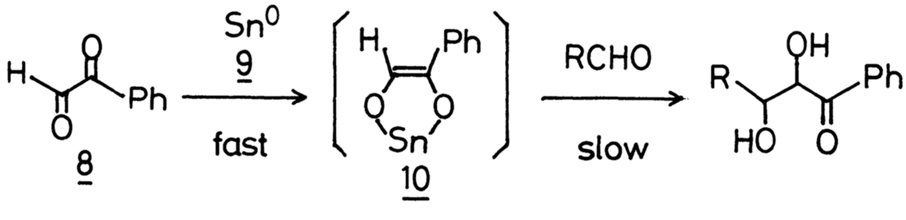
Table I The Synthesis of α,β-Dihydroxy Ketones.[a)]

entry	α-dicarbonyl compound	aldehyde	yield(%)	6 : 7 [b)]
1		$PhCH_2CH_2CHO$	95	1 : 1 [c)]
2		n-$C_8H_{17}CHO$	78	1 : 1 [c)]
3		Me_2CHCHO	83	2 : 1 [d)]
4		$PhCH_2OCH_2CHO$	77	2 : 1 [d)]
5		$PhCH_2CH_2CHO$	92	2 : 1 [c)]
6		n-$C_8H_{17}CHO$	86	2 : 1 [c)]
7		$PhCH_2CH_2CHO$	73	1 : 1 [c)]
8		n-$C_8H_{17}CHO$	68	2 : 1 [c)]

a) All the products gave satisfactory ^{1}H-NMR and IR spectra.
b) The stereochemistry was determined according to Ref.4).
c) Each isomer was isolated.
d) Determined by ^{1}H-NMR.

3-phenylpropanal (67 mg, 0.5 mmol) was added. (The aldehyde was intact in this mixture.) Then a THF (1 ml) solution of 2,3-butanedione (65 mg, 0.75 mmol) was added dropwise, and the reaction mixture was stirred for 2 hr. The mixture was diluted with ethyl acetate and water, and treated with a small amount of aqueous oxalic acid. The precipitates were removed by filtration, and 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. 3,4-Dihydroxy-3-methyl-6-phenyl-2-hexanone (105 mg, 95%) was isolated by thin layer chromatography on silica gel. Bp. 150°C/0.2 mmHg (by bulb to bulb distillation). NMR($CDCl_3$) δ 1.33(3H, s), 1.2-2.0(2H, m), 2.03(3H, s) 2.2-2.9(3H, m), 3.53(1H, m), 3.67(1H, s), 7.07(5H, s). IR(NaCl) 3420, 1710 cm^{-1}.

The results show synthetic utility of the reaction, that is, the present method is effective not only for α-diketones but for α-keto aldehyde (entry 7,8), thus the aldol reaction of tin(II) enediolate, prepared from phenylglyoxal (8), with aldehydes (5) is indeed possible restraining the self-aldol products of active α-keto aldehyde (8). It is presumed that the rate of the oxidative addition of activated metallic tin (9) to α-dicarbonyl compounds (1) is much faster than that of the aldol reaction of tin(II) enediolates (4) with aldehydes (5) (Scheme II).



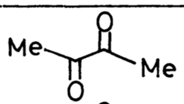
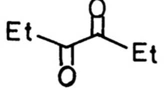
Scheme II

The aldol reaction of enediol-type enolates was found to be a quite useful method for the synthesis of polyoxygenated organic molecules such as sugar derivatives. Though several reports appeared in the investigations on the acylation of tin(IV) enediolates,[5] this is the first example of the aldol reaction of tin(II) enediolates (4).

1,3-Dioxaphosphole, prepared by the reductive treatment of 2,3-butanedione with trimethylphosphite, was already known to react with aldehydes to give 1,3-dioxaphospholanes.[6] Compared with the above mentioned reaction from the synthetic standpoint, the present method has an advantage that the produced organotin compounds are easily hydrolyzed by water to give α,β-dihydroxy ketones (6,7) without accompanying the dehydrated products.

In the next place, the effect of the additive for the improvement of the stereoselectivity was investigated. After screening various additives such as amines, sulfoxides and Lewis acids, it was found that the reaction proceeded rather stereoselectively in the presence of hexafluorobenzene as shown in Table II.

Table II The Aldol Reaction in the Presence of Hexafluorobenzene.[a],[7]

α-dicarbonyl compound	aldehyde	yield(%)	6 : 7[b],[c]
	PhCH$_2$CH$_2$CHO	86	3 : 1
	n-C$_8$H$_{17}$CHO	70	3 : 1
	PhCH$_2$CH$_2$CHO	87	4 : 1
	n-C$_8$H$_{17}$CHO	81	3 : 1

a) All the products gave satisfactory ^{1}H-NMR and IR spectra.
b) The stereochemistry was determined according to Ref.4).
c) Each isomer was isolated.

The role of hexafluorobenzene is not yet clearly known, however, it is supposed that hexafluorobenzene has some interaction with the lone pair of tin(II) or the ene-part of tin(II) enediolates (4), which causes the controlled attack of aldehydes (5). To make these matters clear, a further investigation is now in progress.

References

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5) A. G. Davies and J. A-A. Hawari, J. Organomet. Chem., 224, C 37 (1982); I. Wakeshima and I. Kijima, Bull. Chem. Soc. Jpn., 54, 2345 (1981); See also; W. P. Neumann and A. Schwarz, Angew. Chem., Int. Ed. Engl., 14, 812 (1975).
6) F. Ramirez, A. V. Patwardhan, N. Ramanathan, N. B. Desai, C. V. Greco, and S. R. Heller, J. Am. Chem. Soc., 87, 543 (1965).
7) The reaction was performed in the presence of the equimolar amount of hexafluorobenzene to stannous chloride.

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