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A NEW METHOD FOR THE SYNTHESIS OF β-HYDROXYESTERS BY USING METALLIC TIN

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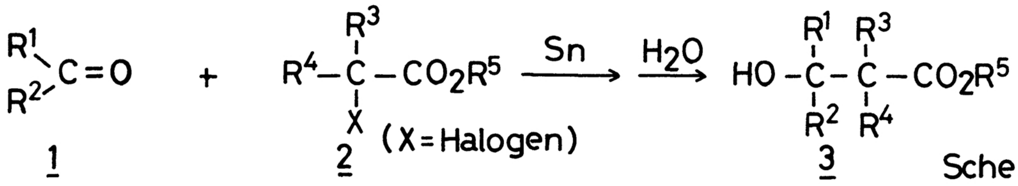
Metallic tin or activated metallic tin, prepared by reduction of stannous chloride with lithium aluminum hydride, smoothly reacts with α-haloesters to yield tin enolates, which in turn react with carbonyl compounds under mild conditions to give, after hydrolysis, β-hydroxyesters in high yields.

The Reformatsky reaction is one of the general methods for the preparation of β-hydroxyesters.1) Under standard conditions, the reactions are carried out in refluxing benzene or benzene/ether solvent system to give the β-hydroxyesters in modest yields at best. One of the major difficulties in carrying out the Reformatsky reaction is initiation of the reaction and then control of the subsequent exothermic reaction. Several major improvements of the standard reaction conditions have recently been published. For example, Rathke et al. have shown that the reaction can be carried out at room temperature in trimethylborate/tetrahydrofuran producing the β-hydroxyesters in high yields.2) Ruppert et al. and Riek et al. have reported improved procedures using a continuous-flow method3) or activated zinc4), respectively, forming β-hydroxyesters in high yields.

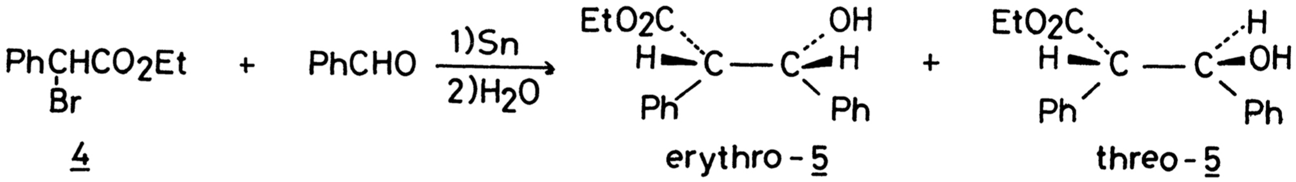
Until recently, synthetic reaction using metallic tin was restricted only to the preparation of dialkyltin dihalide and trialkyltin halide from the reaction of metallic tin and alkyl halide.5) On the other hand, we have recently reported an efficient synthesis of homoallylalcohols by the reaction of allyl halide with carbonyl compounds in the presence of metallic tin.6)

In this communication, we would like to report the reaction of metallic tin or activated metallic tin, prepared by the reduction of stannous chloride with lithium aluminum hydride, with α-haloester 2 to yield an tin enolate, which readily adds to carbonyl compound 1 to give, after hydrolysis, β-hydroxyester 3 in high yield. The overall scheme is shown in Scheme I.



Scheme I

In the first place, the effect of reaction conditions (temperature, solvent and stoichiometric ratio of metallic tin to halide and carbonyl compound) on the yield and stereoselectivity of the present Reformatsky-type reaction was studied. As a model reaction, the synthesis of ethyl 2,3-diphenyl-3-hydroxypropionate 5 from ethyl α-bromophenylacetate 4 and benzaldehyde in the presence of metallic tin (Scheme II) was investigated and the results are shown in Table 1.



Scheme II

Table 1. The Effect of Reaction Conditions on Yield and Stereoselectivity of 5[a)]

Solv.	Temp. (°C)	Time (h)	Yield of 5 (%)	erythro : threo[b)]
DMF	r.t.	0.5	95	80 : 20[c)]
	0	1.0	90	81 : 19
	-45	overnight	78	84 : 16
THF	r.t.	2.0	45	——[d)]
HMPA	r.t.	0.5	92	84 : 16
DMSO	r.t.	0.5	89	83 : 17
PhH	reflux	5.0	94	66 : 34
PhH/Et_2O (1:1)	reflux	5.0	15	——[d)]

a) In all experiments, 1.0 mmol of ethyl α-bromophenylacetate, 1.1 mmol of metallic tin and 0.8 mmol of benzaldehyde were allowed to react in 3 ml of solvent. Commercially available tin was used after treatment as described previously.[5)]

b) The ratio was determined by HPLC analysis. Each compound was separated by preparative TLC and configurational assignment was based on both the coupling constant of the protons at the two asymmetric carbon atoms[7)] and chemical derivation to known 1,2-diphenyl-1-propanol.[8)]

c) When the molar ratio of bromide/Sn/PhCHO=1.0:0.5:0.8, the yield (ratio) of 5 was 69% (83:17).

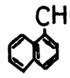
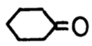
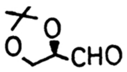
d) Not determined.

As shown in Table 1, the followings are characteristic features of the new Reformatsky-type reaction using metallic tin; (1) It is necessary to use polar solvents such as N,N -dimethylformamide (DMF), dimethylsulfoxide (DMSO) and hexamethylphosphoric triamide (HMPA) to obtain 5 in good yield at room temperature. In benzene, usually employed in the typical Reformatsky reaction, β-hydroxyester 5 is obtained in high yield at reflux temperature, whereas in benzene/ether mixed solvent the reaction is slow. And (2) a rather high stereoselectivity was observed at low temperature to give erythro-5 predominantly.

The results of the reaction between α-halo ester 2 and carbonyl compound 1 are summarized in Table 2. These results show that the reaction is applicable to a wide variety of two components as α-haloesters and carbonyl compounds.

A striking feature of the reaction is revealed when activated tin(=B) prepared from stannous chloride and lithium aluminum hydride (2:1 molar ratio)[9)]was employed. Thus α-chlorophenylacetate reacted with aldehyde to give the corresponding β-hydroxyester 5 in good yield even at room temperature, while no reaction was

Table 2. Reaction of α-Haloesters 2 with Carbonyl Compounds 1a)

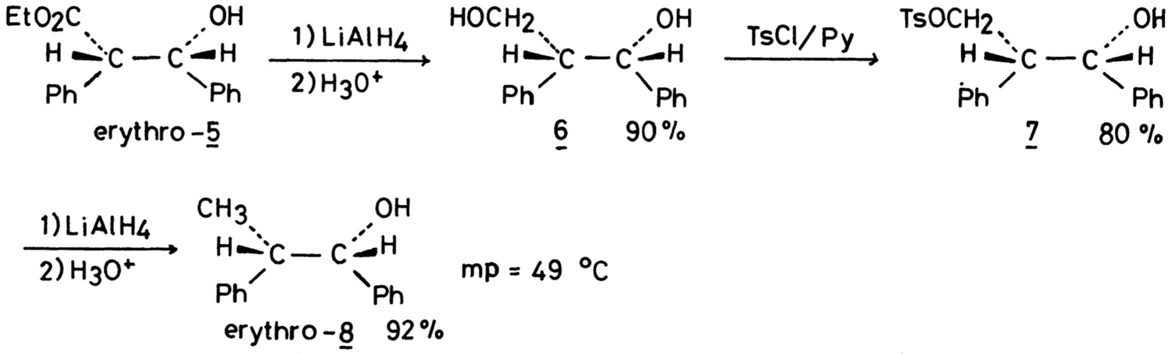
α-Halo ester	Carbonyl compound	Snb)	Solv.	Temp.	Time (h)	Yield (%)	Erythro : Threoc)
$\mathrm{Ph\underset{Br}{C}HCO_2Et}$	p-Cl-PhCHO	A	DMF	r.t.	0.5	88	80 : 20
	p-Me-PhCHO	A	DMF	r.t.	0.5	93	77 : 23
		A	DMF	r.t.	0.5	93	77 : 23
	$\mathrm{PhCH_2CH_2CHO}$	A	DMF	r.t.	0.4	91	71 : 29
	PhCH=CHCHO	A	DMF	r.t.	0.4	83	79 : 21
	$\mathrm{PhCH_2\underset{O}{\overset{}{C}}CH_2Ph}$	B	THF	r.t.	4.0	80d)	
		B	THF	r.t.	2.5	96	
$\mathrm{Ph\underset{Cl}{C}HCO_2Et}$	PhCHO	A	DMF	r.t.	10.0	0	
		B	THF	r.t.	2.0	88	59 : 41
$\mathrm{BrCH_2CO_2Et}$	PhCHO	A	DMF	r.t.	24.0	6	
		B	THF	r.t.	2.0	84	
		B	THF	r.t.	5.0	43e)	
$\mathrm{Me\underset{Br}{C}HCO_2Et}$	PhCHO	B	THF	r.t.	2.0	81	55 : 45
$\mathrm{Et\underset{Br}{C}HCO_2Et}$	PhCHO	B	THF	r.t.	2.5	81	57 : 43
$\mathrm{Me_2\underset{Br}{C}CO_2Et}$	PhCHO	B	THF	r.t.	2.0	95	
$\mathrm{BrCH_2CH{=}CHCO_2Me}$	PhCHO	B	THF	r.t.	2.0	85f)	

a) All the products gave satisfactory NMR and IR spectra.
b) A = the commercially available tin after treatment as described previously.5)
B = the activated tin prepared from stannous chloride and lithium aluminum hydride (2:1 molar ratio). The molar ratio of aldehyde (ketone)/stannous chloride was 0.6 (0.3):1.0.
c) Each compound was separated by preparative TLC and the configurational assignment was based on NMR spectra.
d) 10% of unreacted ketone was recovered.
e) Erythro : threo ratio of ethyl 3,4,5-trihydroxy-4,5-O-isopropylidenepentanoate was 7:3.
f) Erythro : threo ratio (57:43) of the product [=Methyl 2-(α-hydroxybenzyl)-3-butenoate] was evaluated from NMR spectra.

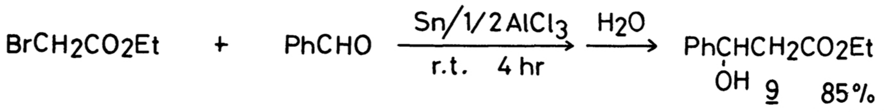
observed when metallic tin(=A) was employed. Similarly, the reaction of ethyl bromoacetate with benzaldehyde in the presence of activated tin(=B) afforded the corresponding β-hydroxyester in good yield, whereas only 6 % of the product was obtained even after long reaction time when metallic tin(=A) was employed. 4-bromocrotonate ester underwent the present reaction exclusively at 2 position to produce the abnormal Reformatsky ester.10)

A typical procedure is described for the preparation of ethyl 3-hydroxy-3-phenylpropionate using activated tin: Lithium aluminum hydride (19 mg; 0.5 mmol) was added portionwise to anhydrous stannous chrolide[11] (190 mg; 1.0 mmol) suspended in THF 1 ml under argon atmosphere. Spontaneous exothermic reaction occured and a dark gray material was deposited. To this suspension, ethyl bromoacetate (100 mg; 0.6 mmol) dissolved in THF 1 ml and subsequently benzaldehyde (53 mg; 0.5 mmol) dissolved in THF 1 ml were added dropwise at room temperature, and the mixtures was stirred for 2 hr at this temperature. Water was added to the reaction mixture and then THF was removed under reduced pressure. The organic materials were extracted with ether and the extract was dried over $MgSO_4$. Ethyl 3-hydroxy-3-phenylpropionate (81 mg, 83%) was isolated by thin layer chromatography on silica gel. NMR ($CDCl_3$) δ 1.17 (3H, t, J = 7 Hz), 2.55 (2H, d, J = 7 Hz), 3.23 - 3.70 (1H, broad), 4.03 (2H, q, J = 7 Hz), 4.93 (1H, t, J = 7 Hz), 7.15 (5H, s). IR (neat) 3450, 1720 cm^{-1}.

References
(1) For a review, see M.W. Rathke, "Organic Reactions", Vol. 22, Wiley, New York (1975), p. 423.
(2) M.W. Rathke and A. Lindert, J. Org. Chem., 35, 3966 (1970).
(3) J.F. Ruppert and J.D. White, J. Org. Chem., 39, 269 (1974).
(4) R.D. Rieke and S.J. Uhm, Synthesis, 1975, 452.
(5) For a example, see K. Sisido, Y. Takeda, and Z. Kinugawa, J. Am. Chem. Soc., 83, 538 (1961).
(6) T. Mukaiyama and T. Harada, Chem. Lett., 1981, 1527.
(7) S.L. Spassov, Tetrahedron, 25, 3631 (1969).
(8) The configurations of erythro-5 and threo-5 were assigned by chemical derivation to known erythro- and threo-1,2-diphenyl-1-propanol, respectively, the mp. and spectra data of which are well known. [D.J. Cram and F.A.A. Elhafez, J. Am. Chem. Soc., 74, 5828 (1952); E.C. Ashby, G.F. Willard, and A.B. Geol, J. Org. Chem., 44, 1221 (1979)]. For example, erythro-5 was converted to erythro-1,2-diphenyl-1-propanol 8 according to the following procedure; (a) reduction of erythro-5 with $LiAlH_4$ to diol 6, (b) monotosylation of diol 6 with p-toluenesulfonylchloride in pyridine to monotosylate 7, and (c) reduction of monotosylate with $LiAlH_4$ to erythro-1,2-diphenyl-1-propanol 8. Mp and spectra data (NMR and IR) of erythro-8 were consistent with reported values. Threo-5 was also converted to threo-8 in 59% overall yield.



(9) The acceleration of the present reaction may be attributed not only to activated tin Sn*, but also to aluminum chloride formed at the same time as shown in the next equation [$SnCl_2 + 1/2LiAlH_4 \rightarrow Sn^* + H_2 + 1/2LiCl + 1/2AlCl_3$]. In fact, ethyl 3-hydroxy-3-phenylpropionate 9 was obtained in good yield from ethyl bromoacetate and benzaldehyde in the presence of metallic tin(=A) and anhydrous aluminum chloride.



$$\mathrm{BrCH_2CO_2Et} \quad + \quad \mathrm{PhCHO} \xrightarrow[\mathrm{r.t.}\ \ 4\,\mathrm{hr}]{\mathrm{Sn/1/2AlCl_3}} \xrightarrow{\mathrm{H_2O}} \mathrm{Ph\underset{OH}{C}HCH_2CO_2Et}$$

9 85%

(10) A.S. Dreiding and R.J. Pratt, J. Am. Chem. Soc., 75, 3717 (1953).
(11) Commercially available stannous chloride was thoroughly dried before use by heating in vacuo at ca. 120°C for an hour.

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