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A NEW METHOD FOR THE REGIO- AND STEREOSELECTIVE SYNTHESIS OF ALDOLS FROM α-BROMOKETONE AND CARBONYL COMPOUNDS BY USING METALLIC TIN

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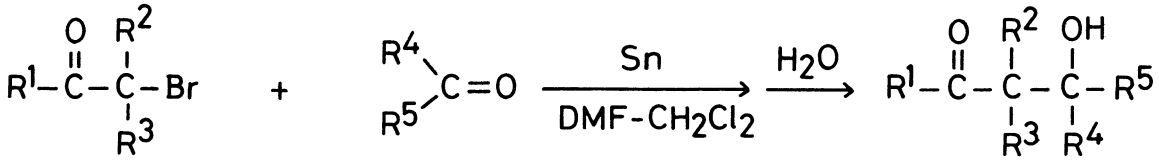
Tin(II) enolates, generated in situ by the oxidative addition of α-bromoketones to metallic tin, react with a variety of carbonyl compounds under mild conditions to give the corresponding aldols in good yields. In the case of reactions of the enolate resulted from α-substituted α-bromoketone with aldehydes, remarkably high *erythro*-selectivities are attained.

Carbon-carbon σ bond formation, one of the most fundamental problems in organic synthesis, is often accomplished by the aldol reaction and much efforts have been devoted to find effective metal enolates useful in the regio- and stereoselective aldol reactions with carbonyl compounds.[1] The most common method for generating metal enolate is based on a metal-hydrogen exchange reaction, and some other methods such as oxidative metallation have also been used occasionally. Recently, an efficient method for the generation of aluminum enolate from α-bromoketone has been disclosed by Nozaki *et al.*[2] It was reported there that the enolate was regioselectively generated by the coupled attack of dialkylaluminum chloride and zinc on the α-bromoketone. According to this procedure, aldol is produced in regioselective manner, however, diastereoselectivity is generally low.

On the other hand, we have already reported that metallic tin or activated metallic tin, prepared in situ by reduction of stannous chloride with lithium aluminum hydride, smoothly reacts with α-haloester to yield the corresponding tin(II) enolate, which in turn reacts with carbonyl compounds under mild conditions to give β-hydroxyesters in high yields.[3] During our continuous investigation on the exploration of new synthetic reaction using metallic tin, we have now found that tin(II) enolate is smoothly generated on treatment of α-bromoketone 1 with



1 2 3

Scheme I

metallic tin.[4] The enolate further reacts with a variety of carbonyl compounds 2 to form aldols 3 at the original site of the bromine of α-bromoketone. The overall scheme is shown in Scheme I. We also report here that the remarkably high *erythro*-selectivity is achieved in the case of reaction of tin(II) enolate resulted from α-substituted α-bromoketone with aldehyde.

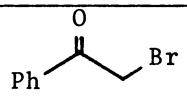
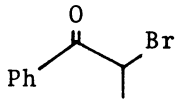
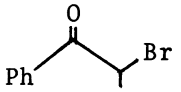
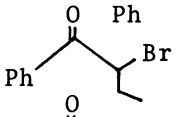
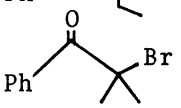
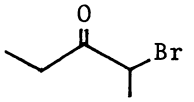
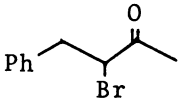
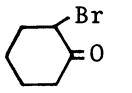
The present new method for aldol reaction was attained *via* two stages (*i.e.* oxidative addition and aldol addition); In the first place, an oxidative addition of α-bromoketone to metallic tin was carried out at -23°C in the case of phenacyl bromide as a starting α-bromoketone in N,N-dimethylformamide(DMF)-dichloromethane mixed solvent, while it was carried out at 0°C in the case of α-bromoketone other than phenacyl bromide. The oxidative addition was enhanced by the presence of catalytic amounts of iodine or sodium iodide in certain case in which less reactive α-bromoketone was used. Time required for the oxidative addition, which could be roughly confirmed by the amount of remaining metallic tin in the reaction mixture, was dependent upon the structure of α-bromoketone used. In general, the time taken to reach this stage was from 0.1 to 10 hr. The successive aldol addition of tin(II) enolate to carbonyl compound to form aldol was carried out at various temperatures as described in the Table. The choice of reaction temperature was based on both the reactivities of the enolate toward carbonyl compounds, and the stereochemical problems involved. Thus, the enolate reacted with various aldehydes smoothly even at -78°C or -45°C to give the corresponding *erythro*-aldols as major diastereomers in good yields, while the reaction with ketones was successfully carried out at 0°C or at room temperature to afford the corresponding aldols.

The regioselectivity of this new aldol reaction was demonstrated by the treatment of tin enolate resulted from 3-bromo-4-phenyl-2-butanone with benzaldehyde to afford the expected β-hydroxyketone (=3-benzyl-4-hydroxy-4-phenyl-2-butanone), without any contamination of the regioisomer.

A typical procedure is described for the reaction of α-bromopropiophenone with p-tolualdehyde; A solution of α-bromopropiophenone (212 mg, 1.0 mmol) in dichloromethane (2 ml) was added dropwise to metallic tin[6] (131 mg, 1.1 mmol) in DMF (2 ml) with stirring under argon at 0°C. The resulting mixture was stirred vigorously at this temperature for 0.6 hr. At this point, the most of the metallic tin disappeared and a dark green slurry resulted. The mixture was cooled to -78°C and a solution of p-tolualdehyde (96 mg, 0.8 mmol) in dichloromethane (2 ml) was added slowly over 20 min. The reaction mixture was stirred for 2 hr at -78°C, then pH 7 phosphate buffer was added. After removal of precipitate by filtration, the organic layer was extracted with ether, and the extract was dried over $MgSO_4$. 3-Hydroxy-2-methyl-1-phenyl-3-(p-tolyl)-1-propanone (201 mg, 99%) was isolated by thin layer chromatography on silica gel (hexane:Et_2O = 4:1); IR (neat) 3450, 1670, 1450, 1220, 970, 700, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.0-7.75 (m, 2 H, aromatic), 7.55-7.0 (m, 7 H, aromatic), 5.1 (d, J=3 Hz, 1 H, *erythro* C*H*OH), 4.9 (d, J=7.5 Hz, trace, *threo* C*H*OH), 3.85-3.5 (m, 2 H, COC*H* and O*H*), 2.3 (s, 3 H, $CH_3\phi$-), 1.15 (d, 3 H, CH_3CH-).

The results are listed in Table. The yields listed in the Table are those after isolation and are based on the starting carbonyl compound.

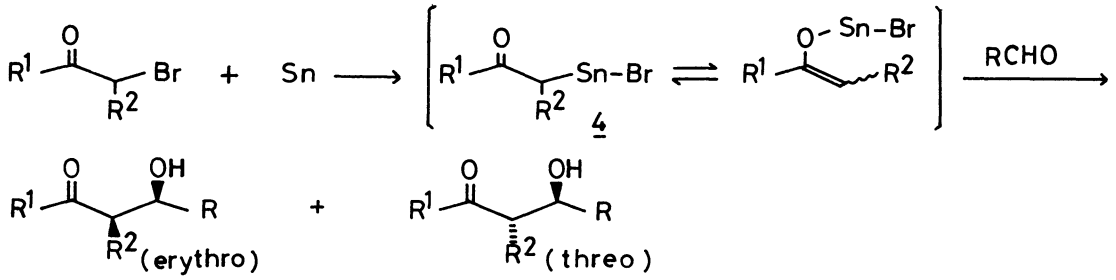
Table. Synthesis of Aldols[a)]

α-Bromoketone	Carbonyl[b)] Compound	Temp.(°C)	Time(hr)	Yield(%)	Erythro:Threo[c)]
	PhCHO	-23	2	63	
	PhCHO	-78	2	93	93 : 7
	p-Me-PhCHO	-78	2	99	92 : 8
	p-Cl-PhCHO	-78	2	91	92 : 8
	$CH_3CH_2CH_2CHO$	-78	2	85	91 : 9[d)]
	$(CH_3)_2CHCHO$	-78	2	72	92 : 8[d)]
		0	2	88	
	$PhCH_2\overset{O}{\overset{\|}{C}}CH_2Ph$	r.t.	16	44[e)]	
	PhCHO	-78	2	82[f)]	
	PhCHO	-78	2	96[f)]	
	PhCHO	-78	2	92	
	$PhCH_2CH_2CHO$	-78	2	94	
	PhCH=CHCHO	-78	2	91	
	PhCHO	-78 -45	2 2	70	91 : 9
	$(CH_3)_2CHCHO$	-78 -45	2 2	65	91 : 9
	$CH_3CH_2CH_2CHO$	-78 -45	2 2	77	92 : 8[g)]
	PhCHO	-78 -45	2 1	82[h)]	> 90 : 10
	PhCHO	-78	5	28	94 : 6

a) All the products gave satisfactory NMR and IR spectra.
b) The molar ratio of α-bromoketone:aldehyde(ketone):Sn = 1.0:0.8(0.5):1.1.
c) Aldol ratio determined by 90 MHz ^1H NMR unless otherwise noted.
d) Aldol ratio determined by ^{13}C NMR.
e) 30 % of unreacted ketone was recovered.
f) Ratio could not be determined by NMR analysis.
g) Aldol ratio determined by 270 MHz ^1H NMR.
h) The reaction was carried out in the presence of catalytic amounts of sodium iodide (0.1 mmol). Product was 3-benzyl-4-hydroxy-4-phenyl-2-butanone.

References

1) For a general discussion, see H. O. House, "Modern Synthetic Reactions", 2nd ed. W. A. Benjamin, New York, N. Y., 1972, pp. 629-732.
2) K. Maruoka, S. Hashimoto, Y. Kitagawa, H. Yamamoto, and H. Nozaki, Bull. Chem. Soc. Jpn., 53, 3301 (1980).
3) T. Harada and T. Mukaiyama, Chem. Lett., 1982, 161.
4) The exact species of the tin enolate in the present reaction is not yet defined clearly, however, we assumed that the divalent tin 4 is probable on the basis of following preliminary experimental facts; (1) As mentioned in the text, most of metallic tin disappeared at the end of the oxidative addition of approximately equimolar amount of α-bromoketone. (2) The divalent species 4 is not so strong enough to reduce another α-bromoketone. In general, α-bromo ketone is not reduced by stannous fluoride and stannous chloride whose reducing powers are assumed to be comparable to the divalent species 4. And (3) high *erythro*-diastereoselectivities were attained in the reaction of the tin enolates resulted from α-branched α-bromoketones with aldehydes, the trend are consistent with our recent result obtained in the stannous triflate mediated cross-aldol reaction *via* divalent tin enolate [T. Mukaiyama, R. W. Stevens and N. Iwasawa, Chem. Lett., 1982, 353]. High *erythro*-selectivities in these two cross aldol reactions *via* divalent species of tin enolate contrast with *threo*-selective cross aldol reaction of tetravalent tin enolate with aldehyde described recently by Stille *et al* [S. Shenvi and J. K. Stille, Tetrahedron Lett., 1982, 627].



5) Commercially available tin powder was treated as described previously [K. Sisido, Y. Takeda, and Z. Kinugawa, J. Am. Chem. Soc., 83, 538 (1961)], and thoroughly dried before use by heating in vacuo at ca. 130°C for an hour.

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