

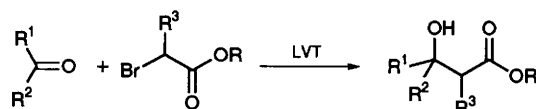
Low-valent Tantalum-mediated Reaction

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Treatment of a mixture of α -halogeno-esters and carbonyl compounds with low-valent tantalum prepared readily from tantalum(v) chloride and activated zinc, afforded β -hydroxy-esters in moderate to good yields.

Though the Reformatsky reaction is an effective method for the synthesis of β -hydroxy-esters, the reaction generally requires drastic conditions (*i.e.* refluxing in benzene, ether or THF).¹ Several improvements have been executed.² Recently, the preparation of β -hydroxy-esters with low-valent metals has been reported. For example, Mukaiyama *et al.* reported an activated metallic tin induced reaction that gave the corresponding β -hydroxy-esters in high yields.³ A Reformatsky type reaction with $\text{Bu}_3\text{SnAlEt}_2$ or $\text{Bu}_3\text{PbAlEt}_2$ was described by Oshima *et al.*⁴ Kagan and coworkers applied samarium(II) iodide to the Reformatsky type reaction of cyclohexanone and ethyl α -bromoacetate.⁵ The reagent is a superior one-electron reducing agent, but it needs care in its use because it is oxidized easily by air. Uchimoto *et al.* described low-valent tantalum (LVT)-induced carbon-carbon bond forming reactions; the dianion equivalent is produced.⁶ We now report the Reformatsky type reactions of α -halogeno-esters with carbonyl compounds with LVT, prepared readily from tantalum(v) chloride and activated zinc dust.



Scheme 1

To find the optimum conditions, we examined the LVT-mediated reaction of ethyl α -bromopropionate with cyclohexanone; entry 8 in Table 1 gives the optimum conditions. Addition of hexamethylphosphoric triamide (HMPA) or tetramethylethylenediamine (TMEDA) was ineffective. The following general procedure was used. To a suspension of the LVT reagent,⁶ prepared from tantalum(v) chloride (3 mmol) and activated zinc dust (4.5 mg atom) in THF (15 cm³) at room temperature, a THF solution (3 cm³) of the α -halogeno-ester (1 mmol) and carbonyl compound (1 mmol) was added at 0 °C under argon. The mixture was stirred at 0 °C for 2 h. After the usual work-up and purification by silica gel column chromatography, the corresponding β -hydroxy-ester was obtained. Other examples are in Table 1.

The reaction of aliphatic cyclic ketones, acyclic ketones, diphenyl ketone and aldehydes with α -bromo-esters in the presence of the LVT reagent easily gave β -hydroxy-esters, but these products were not obtained with α -chloro-esters. The reactions of prochiral carbonyl compounds and ethyl α -bromopropionate gave a mixture of *threo*- and *erythro*-diastereoisomers, with little stereoselectivity. *D*-Camphor was also used as a substrate (entry 8).

Thus the LVT reagent is efficient in Reformatsky type reactions, and its use requires fewer precautions because it is not as sensitive to air as samarium(II) iodide.

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Table 1 The reactions of ethyl α -bromopropionate with ketones and aldehydes in the presence of the LVT reagent

Entry	Carbonyl compound	t/h	Solvent	T/°C	Yield ^a (%) of β -hydroxy-esters
1	Cyclohexanone	2.0	THF	r.t. ^b	67
2	Cyclohexanone	2.0	Benzene	r.t.	Many products
3	Cyclohexanone	2.0	Et ₂ O	r.t.	— ^c
4	Cyclohexanone	2.0	CH ₂ Cl ₂	r.t.	0
5	Cyclohexanone	2.0	MeCN	r.t.	44
6	Cyclohexanone	2.0	DMF	r.t.	Many products
7	Cyclohexanone	2.0	DME	r.t.	78 ^d
8	Cyclohexanone	2.0	THF	0	79
9	Cyclohexanone	2.0	THF	-78	— ^c
10	Cyclohexanone	2.0	THF	Reflux	Many products
11	Cyclohexanone ^e	12	THF	0	40
12	Cyclopentanone	2.5	THF	0	59
13	Acetophenone	2.0	THF	0	81 (17:13) ^{f,g}
14	Benzophenone	2.0	THF	0	62
15	Octan-2-one	2.0	THF	0	75 (3:2) ^{f,g}
16	Cyclohexanone	0.5	THF	0	16 (3:1) ^{f,g} 17 ^h
17	<i>D</i> -Camphor	3.0	THF	0	19 ⁱ
18	Benzaldehyde	1.0	THF	0	75 (<i>threo</i> : <i>erythro</i> = 4:3) ^{f,i}
19	Cyclohexylaldehyde	2.0	THF	0	52 (<i>threo</i> : <i>erythro</i> = 6:5) ^{f,i}
20	Octanal	1.5	THF	0	60 (<i>threo</i> : <i>erythro</i> = 4:3) ^{f,i}

^a Isolated yields. All compounds gave satisfactory ¹H NMR and mass spectral data. ^b Room temp. ^c The reaction mixture coagulated. ^d Yield of the pinacol type coupling product. ^e Reaction with ethyl α -bromoacetate. ^f The *threo*:*erythro* ratio was estimated by ¹H NMR spectral data. ^g The relative configuration of the diastereoisomers could not be determined. ^h Yield of the 1,4-adduct. ⁱ Single enantiomer. ^j The relative configuration was established on the basis of the coupling constants in the ¹H NMR spectra.

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