Low-valent Tantalum-mediated Reaction

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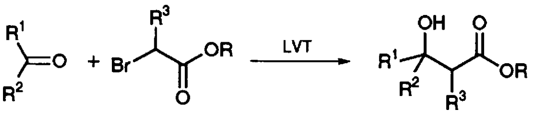
Treatment of a mixture of α-halogeno-esters and carbonyl compounds with low-valent tantalum prepared readily from tantalum(v) chloride and activated zinc, afforded β-hydroxy-esters in moderate to good yields.

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 $Bu_3SnAlEt_2$ or $Bu_3PbAlEt_2$ 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 cm^3) at room temperature, a THF solution (3 cm^3) 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_2O	r.t.	—[c]
4	Cyclohexanone	2.0	CH_2Cl_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	Cyclohexenone	0.5	THF	0	16 (3 : 1)[f,g] 17[h]
17	D-Camphor	3.0	THF	0	19[i]
18	Benzaldehyde	1.0	THF	0	75 (*threo* : *erythro* = 4 : 3)[f,j]
19	Cyclohexylaldehyde	2.0	THF	0	52 (*threo* : *erythro* = 6 : 5)[f,j]
20	Octanal	1.5	THF	0	60 (*threo* : *erythro* = 4 : 3)[f,j]

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[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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