A Preparation of β-Oxoester Enolate Equivalents from $\mathrm{SmI_2}$ and α-Bromoalkanoates

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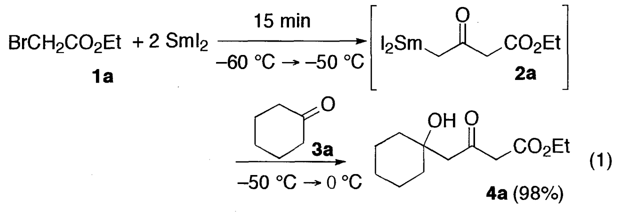
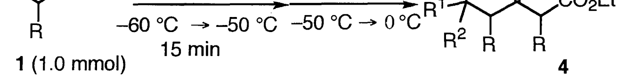
A treatment of ethyl bromoacetate with two molar equivalent of samarium diiodide at –50 °C for 15 min in THF produces a β-oxoester enolate equivalent; the reagent reacts with ketones or aldehydes to give δ-hydroxy-β-oxoesters in excellent yields.

Samarium diiodide ($\mathrm{SmI_2}$) has been recognized to be an effective electron donating reagent in both Reformatsky type reactions[1] and Barbier type reactions.[2] Those have been performed by the treatment of a mixture of carbonyl compounds and organic halides with $\mathrm{SmI_2}$ to produce the corresponding alcohols. Attempts to prepare organosamarium(III) species from $\mathrm{SmI_2}$ and organic halides before an addition of carbonyl compounds, often afforded unsatisfactory results.[3] One of the reasons might come from the instability of samarium(III) species. We assumed that Reformatsky type reagent might be obtained from α-bromoester and $\mathrm{SmI_2}$. In contrast to the assumption, a treatment of cyclohexanone **3a** with a mixture of ethyl α-bromoacetate **1a** and two molar equivalent of $\mathrm{SmI_2}$ gave δ-hydroxy-β-oxoester **4a** in good yield (eq 1). The result suggested the formation of β-oxoester enolate **2a**.[4] This paper describes a novel route to δ-hydroxy-β-oxoester.[5,6]



A solution of ethyl bromoacetate (**1a**, 0.17 g, 1.0 mmol) in THF (3.0 ml) was added to a THF solution of $\mathrm{SmI_2}$ (0.1 M, 20 ml, 2.0 mmol) at –60 °C. The mixture was stirred for 15 min at –50 °C. The color of the reaction mixture turned from dark blue to light yellow during the stirring. A THF solution of cyclohexanone (**3a**, 0.5 g, 0.5 mmol) was added to the reaction mixture. The resulting mixture was stirred for 15 min at the same temperature and for another 15 min at 0 °C. The reaction mixture was worked up with aqueous condition and the crude product was purified by silica gel column chromatography; ethyl 5-(1-hydroxycyclohexyl)-3-oxobutanoate **4a** was obtained in 98% yield (112 mg). Other carbonyl compounds afforded corresponding δ-hydroxy-β-oxoesters in good yields; the results are summarized in Table 1. Benzaldehyde, that is easily reduced with $\mathrm{SmI_2}$, also gave the corresponding product in high yield (entry 9). The use of α,β-unsaturated aldehyde gave the 1,2-adduct exclusively (entry 10). The results showed a complete consumption of $\mathrm{SmI_2}$ before an addition of aldehyde under the reaction conditions. The intermediate **2a** also added to β-tetralone to give the corresponding product in good yield (entry 5).[7]

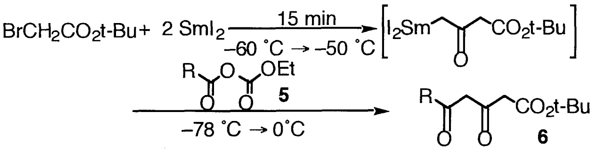
Table 1. Preparation of δ-Hydroxy-β-ketoesters by Self-condensed Reformatsky Type Reagent [a]

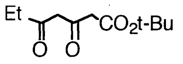
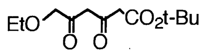
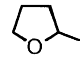
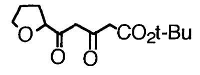


Entry	R	Carbonyl compound	Time / h	Yield / % [b]
1	H	Cyclohexanone	0.5	98
2	H	Cyclopentanone	1.0	>98
3	H	Propanal	1.0	87
4	H	4-Heptanone	1.0	>98
5	H	β-Tetralone	0.5	82
6	H	2-Methylcyclohexanone	1.0	95 (10 / 90)[c]
7	H	4-t-Butylcyclohexanone	1.0	>98 (12 / 88)[c]
8	Me	Cyclohexanone	0.2	95[d]
9	H	Benzaldehyde	0.5	>98
10	H	(E)-2-Hexenal	0.5	>98

a) β-Hydroxyester was not detected by nmr in all cases. b) Isolated yield. c) A ratio of diastereomers. d) Isolated as a diastereomeric mixture.

Table 2. Preparation of t-Butyl 3,5-Diketoalkanoate[a]



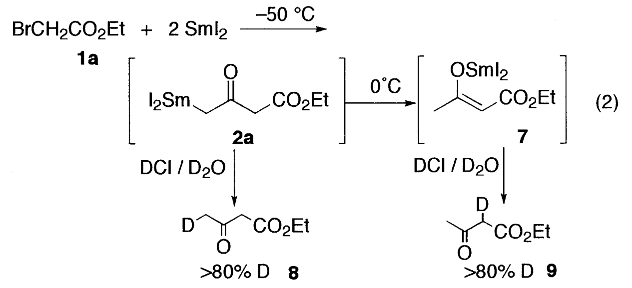
Entry	R	Yield / %[b]	Product
1	Et-	26[c]	
2	$\mathrm{EtOCH_2}$-	65	
3		75	

a) $\mathrm{BrCH_2CO_2t\text{-}Bu}$ (1.0 mmol), $\mathrm{SmI_2}$ (2.0 mmol), and anhydride (0.48 mmol) were used. b) Isolated Yield. c) t-Butyl 4-ethoxycarbonyl-3-oxobutanoate was also isolated in 23% yield.

The intermediate **2** was effective to give diketo ester **6** by the reaction with the mixed anhydrides **5**[8] as shown in Table 2.[9] In these cases, the intermediate was prepared by a condensation of the t-butyl ester that are often tolerate to nucleophilic attack.

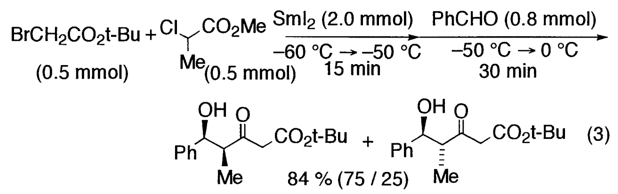
In these reactions, alkoxy group on the substrate (ethoxy and tetrahydrofuranyl in entries 2 and 3) promoted the reaction.[10]

The intermediate **2** was stable under –50 °C, but the thermal isomerization was observed when the temperature of reaction mixture was raised to 0 °C. Quenching the reagent at –50 °C with DCl in D_2O afforded 4-deuterio compound **8** quantitatively (eq 2). In contrast, after the reagent was warmed up to 0 °C, quenching it with DCl in D_2O afforded 2-deuterio compound **9** quantitatively. The intermediate **2a** isomerized into the stable enolate 7 that did not give any adduct with ketone or aldehyde.[11]



(2)

An attempt of cross condensation was also realized by a proper combination of α-haloesters. An equimolar mixture of methyl 2-chloropropionate and t-butyl bromoacetate was treated with SmI_2 and followed by an addition of benzaldehyde; t-butyl 5-hydroxy-5-phenyl-3-ketopentanoate was isolated in 84% yield as a diastereomeric mixture (eq 3).[12]



(3)

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6 A part of the results described here has been reported; the 40th Symposium on Organometallic Chemistry, Japan, Sapporo, 1993, Abstr., PB109; the 67th Annual Meeting of the Chemical Society of Japan, Tokyo, 1994, Abstr., 4J228.

7 The dianion, obtained from ethyl acetoacetate and lithium diisopropylamide,[5] acted as a strong base to β-tetralone and resulted in an enolization.

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