



Intramolecular and intermolecular ketone–ester reductive coupling reactions promoted by samarium(II) iodide

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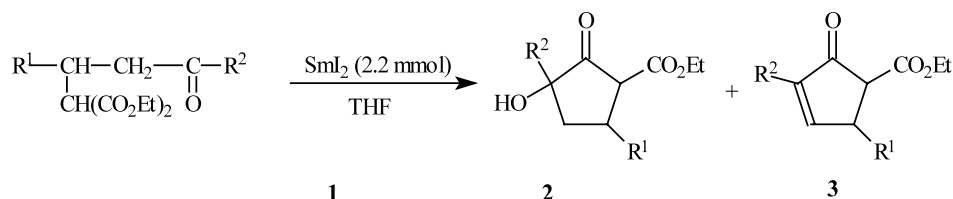
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Abstract—Intramolecular and intermolecular ketone–ester reductive coupling reactions promoted by SmI₂ have been studied. Substituted 2-hydroxy-5-ethoxycarbonylcyclopentanones, 5-ethoxycarbonylcyclopentenones and α-ketols were prepared in moderate to good yields at room temperature or under reflux under neutral conditions. © 2001 Elsevier Science Ltd. All rights reserved.

Carbon–carbon bond formation is the essence of organic synthesis and reductive couplings are amongst the most valuable methods for making carbon–carbon bonds. Since pioneering studies by Kagan and following investigations by other scientists, SmI₂ has been shown to be an exceedingly reliable, mild, neutral, selective and a versatile single electron transfer reagent for promoting reductive coupling reactions.¹ For instance, Barbier reactions,² Reformatsky reactions,³ pinacol coupling reactions⁴ and ketyl–olefin coupling reactions⁵ have been reported using SmI₂ as the reagent. It is well known that the Barbier-type reactions of organic halides with esters promoted by SmI₂ and the reductive coupling of ketones with esters induced by low valent titanium have been widely documented.^{6,7} However, to the best of our knowledge, there is no literature report on the reductive coupling reaction of ketones with esters promoted by SmI₂. Recently, we reported intermolecular and intramolecular ketone–nitrile cross-coupling reactions promoted by SmI₂.⁸

Now, we wish to describe our preliminary results on a novel keto-ester reductive cross-coupling reaction promoted by SmI₂ (Scheme 1).

Substrates **1**, which possess a carbonyl group and two ethoxycarbonyl groups, undergo intramolecular cross-coupling reactions even at room temperature under a nitrogen atmosphere. The reductive cyclization products, substituted 2-hydroxy-5-ethoxycarbonylcyclopentanones **2**, were obtained in moderate to good yields at room temperature. Interestingly, when the reaction was carried out at reflux, substituted 5-ethoxycarbonylcyclopentenones **3** were obtained as the major products along with smaller amounts of products **2**. These results are different from those obtained using low valent titanium, which produce deoxygenated products.⁷ Table 1 summarizes the results of the intramolecular cyclization of keto-diester **1**. The reaction is highly chemoselective, only cyclization products were obtained, while



Scheme 1.

Keywords: ketone; ester; reductive coupling; samarium(II) iodide; 2-hydroxy-5-ethoxycarbonylcyclopentanones; 5-ethoxycarbonyl cyclopentenones; α-ketols.

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pinacol coupling products of the ketones were not detected. In this reaction, substituents such as chloro and alkoxy groups are not reduced.⁹

In order to check the reactivity of SmI₂ for keto-ester reductive coupling, we further studied the intermolecular reaction of ketones or aldehydes **4** with esters **5** induced by SmI₂, affording α -ketols **6** and/or pinacols **7** (Scheme 2).

Table 2 summarizes our results on the ketone-ester reductive couplings. Refluxing conditions are necessary for better yields. If the reaction was carried out at room temperature, it was slow and gave lower yields (entry 1). Table 1 shows that both aromatic and aliphatic

ethyl esters are suited for the reaction. However, they need longer when the latter are used and afford the products in lower yields than those of the former (entry 5). As for ketones **1**, when benzophenone was used, the reaction gave α -ketols **6** in moderate yields. For comparison, treatment of aromatic aldehydes and esters with SmI₂ at room temperature, even under reflux, did not give α -ketols **6**, only pinacol coupling products **7** in good yields (entry 8). Treatment of acetophenone and ethyl benzoate with SmI₂, gave α -ketol **6** along with pinacol **7** (entry 9).

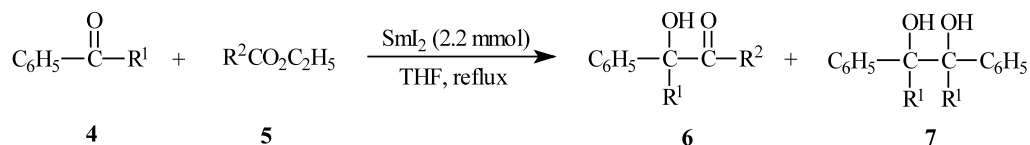
A possible mechanism for the formation of substituted 2-hydroxy-5-ethoxycarbonylcyclopentanones and α -ketols is described in Scheme 3.

Table 1. Intramolecular reductive coupling of keto-diester **1**

Entry	R ¹	R ²	T (°C)	Reaction time (h)	Yield (%) ^{a,b}	
					2	3
1	C ₆ H ₅	C ₆ H ₅	Rt	4	68 (2a)	–
			65	5	10	55 (3a)
2	4-ClC ₆ H ₄	C ₆ H ₅	Rt	4	69 (2b)	–
			65	5	12	54 (3b)
3	4-CH ₃ C ₆ H ₄	C ₆ H ₅	Rt	4	70 (2c)	–
			65	5	11	57 (3c)
4	3,4-OCH ₂ OC ₆ H ₃	C ₆ H ₅	Rt	5	63 (2d)	–
			65	6.5	15	45 (3d)
5	4-ClC ₆ H ₄	4-CH ₃ C ₆ H ₄	Rt	3.5	69 (2e)	–
			65	4.5	13	51 (3e)
6	C ₆ H ₅	4-CH ₃ C ₆ H ₄	Rt	4	70 (2f)	–
			65	5	8	60 (3f)

^a Isolated yields.

^b 2.2 mmol SmI₂ and 1 mmol of **1** were used.



Scheme 2.

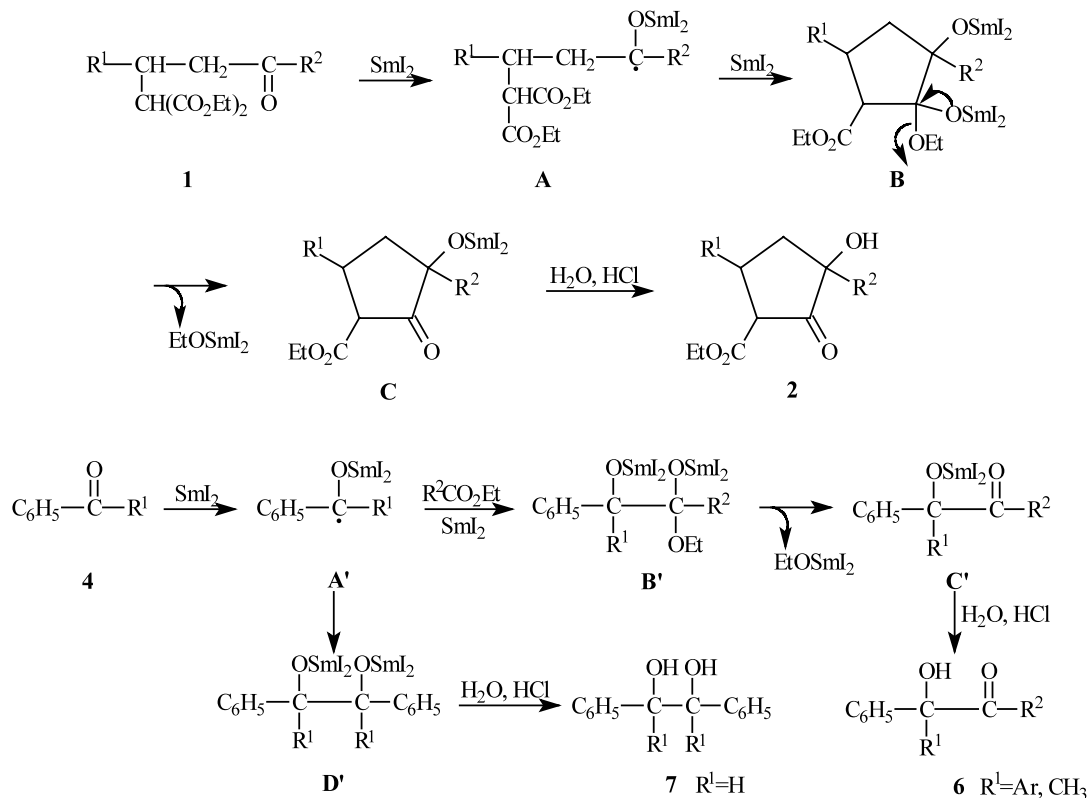
Table 2. The intermolecular reductive coupling of ketones with esters

Entry	R ¹	R ²	Reaction time (h)	Yield (%) ^a	
				6	7
1	C ₆ H ₅	C ₆ H ₅	5 (24 ^c)	68 ^b , 37 ^c	–
2	C ₆ H ₅	4-CH ₃ C ₆ H ₄	5	62 ^b	–
3	C ₆ H ₅	4-CH ₃ OC ₆ H ₄	6	61 ^b	–
4	C ₆ H ₅	4-ClC ₆ H ₄	5.5	63 ^b	–
5	C ₆ H ₅	<i>n</i> -C ₃ H ₇	9	45 ^b	–
6	4-CH ₃ C ₆ H ₄	C ₆ H ₅	3	65 ^b	–
7	4-CH ₃ OC ₆ H ₄	C ₆ H ₅	4	60 ^b	–
8	H	C ₆ H ₅	7	–	82 ^c , 84 ^c
9	Me	C ₆ H ₅	9	28 ^b	45 ^b

^a Isolated yields.

^b Reaction was carried out under reflux.

^c Reaction was carried out at room temperature.



Scheme 3.

In the intramolecular (or intermolecular) keto-ester coupling reaction, after the formation of ketyl anion A (or A'), ring closure occurs (or intermediate B' forms) via radical addition onto the ethoxycarbonyl group. Sequential transformations led to the target products. In the intermolecular cross-coupling reaction, when aldehydes were used, the pinacol coupling reaction could proceed prior to the aldehyde-ester reaction because the ketyl radical from aromatic aldehydes is more reactive.

In summary, novel reductive cross-coupling reactions of ketones with esters were successfully achieved with the aid of samarium(II) iodide. Substituted 2-hydroxy-5-ethoxycarbonylcyclopentanones, 5-ethoxycarbonylcyclopentenones, and α -ketols have been prepared in moderate to good yields.

Acknowledgements

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- General procedure: A solution of substrate **1** (1 mmol) in THF (2 mL) was added to SmI₂ (2.2 mmol) at room temperature under a nitrogen atmosphere. The mixture was then stirred under these conditions until the reaction was completed (Table 1). The reaction was quenched with dilute HCl (1 M, 1 mL) and extracted with ether. After the usual work-up, the crude product was purified by preparative TLC (ethyl acetate:cyclohexane, 1:6) to give **2** and **3**. The physical data of new compounds are listed. Compound **2c**, mixture of stereoisomers. ν_{\max} : 3450 (OH), 1750

(C=O), 1714 (C=O) cm^{-1} . δ_{H} : 7.70–6.95 (9H, m, ArH), 4.26–3.88 (3H, m, OCH_2 , OH), 3.64–3.20 (2H, m, ring CH, CH), 2.50–1.78 (5H, m, ArCH_3 , ring CH_2), 1.26–0.98 (3H, m, CH_3). m/z (%): 338 (M^+ , 1.26), 320 (12), 291 (20.02), 217 (21.49), 105 (100). Anal. $\text{C}_{21}\text{H}_{22}\text{O}_4$. Calcd C, 74.54; H, 6.55. Found C, 74.46; H, 6.49. Compound **3c**, mixture of stereoisomers. ν_{max} : 3080, 3020,

1750 (C=O), 1690 (C=O), 1647 (C=C) cm^{-1} . δ_{H} of major isomer: 7.83–7.06 (10H, m, ArH, =CH), 4.53–4.18 (3H, m, ring CH, OCH_2), 3.52 (1H, d, $J=12.0$ Hz, ring CH), 2.33 (3H, s, ArCH_3), 1.26 (3H, t, $J=7.2$ Hz, CH_3). m/z (%): 320 (M^+ , 34.3), 275 (18.74), 246 (100). Anal. $\text{C}_{21}\text{H}_{20}\text{O}_3$. Calcd C, 78.73; H, 6.29. Found C, 78.85; H, 6.23.