

One-pot Preparation of β -Hydroxy Esters Catalysed by a Bis(cyclopentadienyl)titanium(IV) Dichloride–Zinc System

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The reaction of α -haloesters with carbonyl compounds catalysed by $\text{Cp}_2\text{TiCl}_2(\text{cat.})\text{-Zn}$ gives β -hydroxy esters.

The Reformatsky reaction is one of the most useful methods for the formation of C–C bonds. The reaction has been modified in many ways to improve both the yield and the purity of the β -hydroxy esters.^{1–5} Herein, we report a novel

reaction catalysed by $\text{Cp}_2\text{TiCl}_2\text{-Zn}$ in tetrahydrofuran (THF) or diethyl ether that gives the same product as the Reformatsky reaction in high yield under mild conditions.

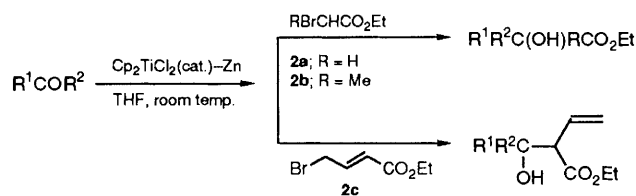
In a typical procedure, into a mixture of acetophenone (2.4 g, 20 mmol) and bis(cyclopentadienyl)titanium(IV) dichloride (0.11 g, 0.44 mmol) in THF (5 ml) were added ethyl bromoacetate **2a** (22 mmol, 2.4 ml) and zinc dust (0.65 g, 10 mmol) at room temperature and the mixture stirred for 2 min during which period the initial red suspension turned to a green one. After about 5 min, the unreacted zinc dust was removed by filtration and the filtrate afforded, after the usual purification, β -hydroxy ester **3** (Table 1, entry 4) in 95% yield.

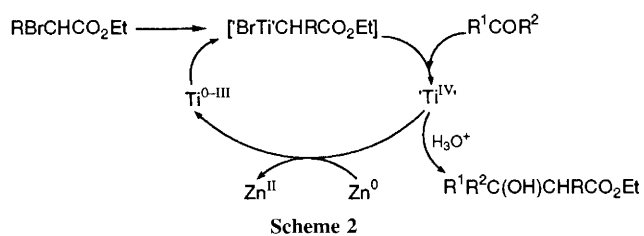
Comparison with the most efficient method for the Reformatsky reaction of bromoacetate with benzaldehyde or cyclohexanone showed that our modified method has the following advantages:⁶ (i) pretreated anhydrous solvent was not required and (ii) an over-elaborate procedure for the activation of zinc was not necessary. Diastereoselectivity in our method was low and in the case of γ -bromocrotonate the allylic rearrangement product was obtained exclusively.

Table 1 The reaction of α -haloester with carbonyl compound in $\text{Cp}_2\text{TiCl}_2(\text{cat.})\text{-Zn-THF}$ system

Entry	RX	Carbonyl compound	t/min	Yield (%) ^{a,b}	<i>erythro</i> : <i>threo</i>
1	2a	PhCHO	5	90	
2	2a	Pr ⁱ CHO	4	80	
3	2a	Cyclohexanone	5	81	
4	2a	Cyclopentanone	5	70	
5	2a	PhCOMe	5	95	
6	2b	Pr ⁿ CHO	4	88	57:43 ^c
7	2b	PhCHO	5	90	40:60 ^d
8	2b	PhCOMe	6	96	
9	2b	Cyclohexanone	5	80	
10	2c	PhCHO	8	87	50:50 ^e
11	2c	PhCOMe	8	65	

^a Purified by column chromatography on silica (eluent: light petroleum–ethyl acetate). ^b All products gave satisfactory IR and NMR data which are consistent with those of authentic samples. ^c Determined by ¹H NMR (600 MHz) δ 3.90 (2 \times t, 1 H, *erythro*, J 3.78 and 8.64 Hz) and 3.76 (m, 1 H, *threo*). ^d Determined by ¹H NMR (600 MHz) δ 5.08 (d, 1 H, *erythro*, J 4.26 Hz) and 4.74 (d, 1 H, *threo*, J 8.39 Hz). ^e Determined by ¹H NMR (600 MHz) δ 3.32 (dd, 1 H, *erythro*, J 6.2 and 8.9 Hz) and 3.42 (t, 1 H, *threo*, J 8.3 and 8.3 Hz).





Although the role of bis(cyclopentadienyl)titanium(IV) dichloride is still not clear, it is likely that reduction of titanium(IV) with zinc dust provides low valent titanium,⁷ which reacts with the α -halo ester to give the corresponding metal-reagent, which then reacts with the carbonyl compound

to give the β -hydroxy ester. The reaction mechanism is probably as shown in Scheme 2.

Received, 13th January 1992; Com. 2/00137C

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