

A General Method for the Formation of Zinc Enolate Equivalents from Iodoacetates by Diisopropylzinc-Iodine Exchange Reaction: Preparation of β -Hydroxy Esters

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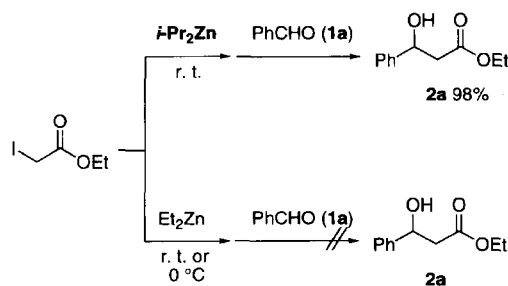
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Diisopropylzinc is found to be a highly efficient reagent for the formation of zinc enolate equivalents from various iodoacetates via iodine-zinc exchange reaction at room temperature, affording β -hydroxy esters in high yields by the reaction with aldehydes and ketones.

The Reformatsky reaction is a very important process for the preparation of β -hydroxy esters from α -halo esters, zinc metal and carbonyl compounds.¹ The oxidative insertion of zinc metal (powder) to α -haloester forms a zinc enolate equivalent, which then reacts with carbonyl compounds. However, most of the formation process of zinc enolate equivalents is heterogeneous because zinc powder is not soluble in organic solvent. Moreover, some special protocols are often required, such as the activation of zinc powder,² heating, and the use of polar solvents.³ On the other hand, the formation of ester enolate equivalents by the halogen-zinc exchange reaction using dialkylzinc is advantageous because the reaction proceeds in a homogeneous manner. Although the formation of enolate equivalents from α -halo ketones by diethylzinc-halogen exchange reaction is known,^{4a,4b} ethyl bromoacetate does not form an enolate equivalent by diethylzinc-halogen exchange.^{4a} In our hands, β -hydroxy ester was not obtained via the formation of zinc enolates from zinc-iodine exchange reaction using *diethylzinc* and *ethyl* iodoacetate, a representative iodoacetate (Scheme 1, lower equation).⁵ To the best of our knowledge, in the diethylzinc-iodine exchange reaction, the structure of iodoacetates which could be utilized has been limited to those of the sterically bulky esters such as *t*-butyl^{6a} and benzyl^{6b} iodoacetates. Thus the development of a generalized procedure for the dialkylzinc-iodine exchange reaction of iodoacetates is a challenge.

We here report that *diisopropylzinc* (*i*-Pr₂Zn)⁷ effectively forms zinc enolate equivalents from various iodoacetates in-

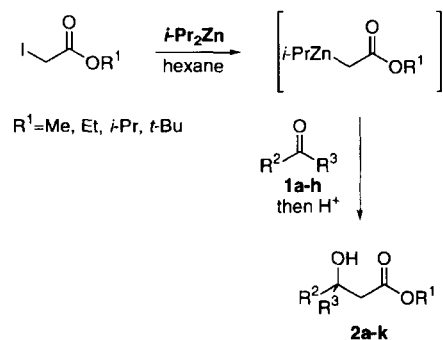


Scheme 1.

cluding ethyl ester by *i*-Pr₂Zn-iodine exchange reaction, and that the subsequent reaction with carbonyl compounds affords various β -hydroxy esters in high yields (Scheme 1, upper equation). The reaction could be carried out at room temperature or at 0 °C. The process constitutes a convenient and general method for the preparation of β -hydroxy esters (Scheme 2).


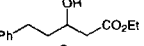

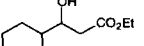
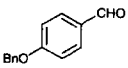
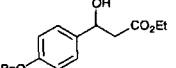
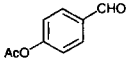
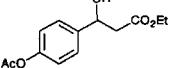
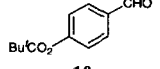
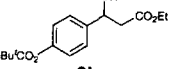

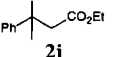
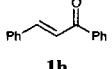
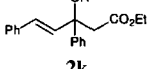
By employing a hexane solution of *i*-Pr₂Zn,⁷ the zinc enolate equivalent from ethyl iodoacetate was successfully formed at room temperature. Subsequent reaction with benzaldehyde **1a** afforded the corresponding β -hydroxy ester, ethyl 3-hydroxy-3-phenylpropanoate **2a**, in 98% yield (Table 1, Entry 1). Methyl iodoacetate, by the treatment with *i*-Pr₂Zn and the subsequent reaction with aldehyde **1a** at 0 °C, also afforded β -hydroxy ester **2b** in 99% yield (Entry 3). In addition to methyl and ethyl iodoacetates, isopropyl and *t*-butyl iodoacetates also afforded the corresponding β -hydroxy esters **2c** and **2d** in 98 and 99% yields, respectively (Entries 4 and 5). When methyl iodoacetate was reacted with *i*-Pr₂Zn, the reaction was quenched by the addition of water. ¹H NMR analysis of the mixture revealed the complete consumption of methyl iodoacetate and the clean formation of methyl acetate. The result shows that zinc enolate equivalent forms from methyl iodoacetate and *i*-Pr₂Zn. As described above, *i*-Pr₂Zn was found to be an efficient reagent for the formation of zinc enolate equivalents from various iodoacetates.

The generality of carbonyl compounds is exemplified in the reactions with zinc enolate equivalents derived from ethyl iodoacetate and *i*-Pr₂Zn. Reactions with aliphatic aldehydes (possessing hydrogen atom(s) on the α -carbon atom) such as 3-phenylpropanal **1b** and cyclohexanecarbaldehyde **1c** gave β -hydroxy esters **2e** and **2f** in the yields of 99 and 87%, respectively (Entries 6 and 7). The ester groups remained



Scheme 2.

Table 1. Synthesis of β -Hydroxyesters from Iodoacetates, Diisopropylzinc, and Carbonyl Compounds

Entry ^{a)}	Carbonyl compounds	R ¹	β -Hydroxyesters	Isolated yield/%
1	PhCHO 1a	Et	PhCH(OH)CH ₂ CO ₂ Et 2a	98
2 ^{b)}		Et		99
3 ^{c)}		Me	PhCH(OH)CH ₂ CO ₂ Me 2b	99
4		Pr ⁱ	PhCH(OH)CH ₂ CO ₂ Pr ⁱ 2c	98
5		Bu ⁱ	PhCH(OH)CH ₂ CO ₂ Bu ⁱ 2d	99
6 ^{b)}		Et		99
7 ^{b)}		Et		87
8 ^{b)}		Et		99
9 ^{b)}		Et		99
10 ^{b)}		Et		99
11		Et		77 ^{d)}
12		Et		84

a) Unless otherwise noted, iodoacetate was treated with *i*-Pr₂Zn at room temperature for 4 h. Molar ratio. Carbonyl compound : iodoacetate : *i*-Pr₂Zn = 1 : 1.5 : 2.1 b) Molar ratio, 1 : 3.5 : 5. c) Iodoacetate was treated with *i*-Pr₂Zn at 0 °C for 0.5 h d) Accompanied with 18% of an aldol product of **1g**.

intact during the reaction, and the β -hydroxy esters **2h** and **2i** possessing ester groups were obtained in 99% yield (Entries 9 and 10). Ketones also can be employed. The addition to acetophenone **1g** gave **2j** in 77% (Entry 11), and the reaction with α,β -unsaturated ketone **1h** proceeded in a 1, 2-addition manner to afford β -hydroxy ester **2k** in 84% yield (Entry 12).

In conclusion, we have developed a convenient method for the formation of zinc enolate equivalents from general iodoacetates by diisopropylzinc-iodine exchange reaction. The subsequent addition reaction to the carbonyl compounds gave β -hydroxy esters in high yields.

Experimental

A Representative Procedure for the Preparation of β -Hydroxy esters 2 (Table 1, Entry 1): To a 1 M (M = mol dm⁻³) hexane solution (2.1 mL) of *i*-Pr₂Zn (2.1 mmol) was added ethyl iodoacetate (321 mg, 1.5 mmol) under an argon atmosphere at room temperature. The mixture was stirred for 4 h at room temperature. Then, benzaldehyde **1a** (106 mg, 1.0 mmol) was added at 0 °C and the mixture was stirred for 20 h. The reaction was quenched by the addition of satd. aqueous ammonium chloride and the mixture

was extracted with diethyl ether. The extract was dried over anhydrous sodium sulfate and concentrated under reduced pressures. Purification of the residue on silica-gel thin-layer chromatography afforded **2a** (189 mg) in 98% yield.

Ethyl 3-[4-(2,2-Dimethylpropanoyloxy)phenyl]-3-hydroxypropanoate (2i). Mp 68.5 °C (hexane); ¹H NMR (300 MHz, CDCl₃) δ = 1.24 (3H, t, *J* = 7.1 Hz), 1.35 (9H, s), 2.68 (1H, dd, *J* = 16.4, 4.7 Hz), 2.71 (1H, dd, *J* = 16.4, 8.0 Hz), 3.41 (1H, s), 4.18 (2H, q, *J* = 7.1 Hz), 5.12 (1H, dd, *J* = 8.0, 4.7 Hz), 7.05 (2H, d, *J* = 8.5 Hz), 7.37 (2H, d, *J* = 8.5 Hz); ¹³C NMR (75 MHz, CDCl₃) δ = 14.1, 27.1, 39.0, 43.3, 60.9, 69.8, 121.5, 126.7, 139.8, 150.5, 172.3, 177.1; IR (KBr) 3456, 1759 cm⁻¹. Found: C, 65.14; H, 7.51%. Calcd for C₁₆H₂₂O₅: C, 65.29; H, 7.53%.

Ethyl (4E)-3-Hydroxy-3,5-diphenylpent-4-enoate (2k). Mp 89–90 °C (hexane); ¹H NMR (300 MHz, CDCl₃) δ = 1.16 (3H, t, *J* = 7.1 Hz), 3.01 (1H, d, *J* = 15.7 Hz), 3.03 (1H, d, *J* = 15.7 Hz), 4.09 (2H, q, *J* = 7.1 Hz), 4.85 (1H, s), 6.42 (1H, d, *J* = 16.0 Hz), 6.65 (1H, d, *J* = 16.0 Hz), 7.2–7.6 (10H, m); ¹³C NMR (75 MHz, CDCl₃) δ = 14.0, 45.2, 61.0, 74.9, 125.2, 126.6, 127.2, 127.6, 128.4, 128.5, 134.0, 136.5, 144.5, 172.5; IR (KBr) 3509, 1701 cm⁻¹. Found: C, 77.03; H, 6.92%. Calcd for C₁₉H₂₀O₃: C, 77.00; H, 6.80%.

β -Hydroxy esters **2a**, ^{2b} **2b**, ^{8a} **2c**, ^{8b} **2d**, ^{8c} **2e**, ^{8a} **2f**, ^{8d} **2g**, ^{8e} **2j**^{1c} are known compounds.

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