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Indium Mediated Reactions In Water: Synthesis of β-Hydroxyl Esters

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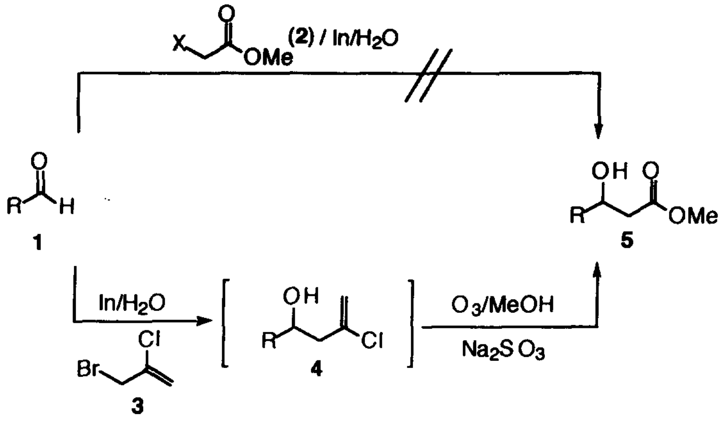
Summary. *A variety of β-hydroxyl esters were synthesized efficiently through indium mediated carbon-carbon bond formation in water followed by ozonolysis.* © 1997 Elsevier Science Ltd.

β-Hydroxyl carboxylic esters are important intermediates for various natural product syntheses. Such compounds are generally synthesized through the traditional Reformatsky reaction in which an aldehyde or ketone is treated with zinc and an α-halo ester.[1] A prime requirement of the traditional Reformatsky reaction is the exclusion of water.[2] A useful alternative to the Reformatsky reaction as a means of preparing β-hydroxyl carboxylic esters involves the reaction of aldehyde (ketone) with carboxylate enolate[3] (or the Mukaiyama's silyl ketene acetal reaction).[4] Such a process equally requires the strict exclusion of moisture. In both cases, other functionalities, such as a hydroxyl group, existed in the same molecule would have to be protected (and later deprotected) prior to the reaction.

Recently, Barbier-Grignard type carbon-carbon bond formation in aqueous medium has attracted many interests, partly due to the prospects of simplifying protection-deprotection processes in complex synthesis.[5] To effect such reactions, indium has shown to be an important mediator.[6] The aqueous reactions have been shown to be particularly effective in the synthesis of polyhydroxylated[7] and medium ring compounds.[8] In an effort to synthesize biologically important polyhydroxylated carboxylic acid derivatives, we needed to develop a general and effective methodology for the preparation of β-hydroxyl carboxylic esters with which compounds bearing functional groups can be used directly without the necessary employment of protection-deprotection steps. Toward this objective, we initially investigated the direct coupling of aldehydes with an α-halo ester mediated by indium metal in aqueous medium. While the direct reaction between an aromatic aldehyde and a secondary or a tertiary α-halo ester mediated by metals such as Zn[9] or Sn[10] in aqueous medium has been known to give low yield of the product, aliphatic aldehydes or primary α-halo esters generally do not react under such reaction conditions. No apparent reaction was observed during our investigation with indium with these substrates either. On the other hand, it was found that various aldehydes can be alkylated with 3-bromo-2-chloro-1-propene (**3**) very efficiently mediated by indium in water at room temperature. The reaction provided clean product **4** as shown by TLC and ^{1}H NMR measurements. Subsequent treatment of the compound **4** with ozone in methanol followed by work-up with sodium sulfite provided the desired hydroxyl ester in high yield (Scheme 1). The diminished yields in some cases are mainly due to isolation losses incurred during the work-ups of two steps.



Scheme 1.

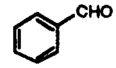
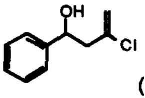
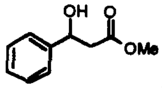
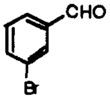
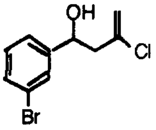
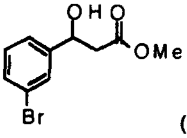
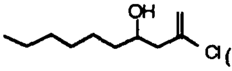
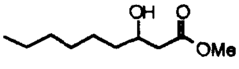
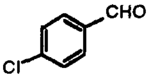
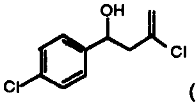
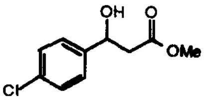
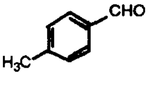
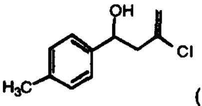
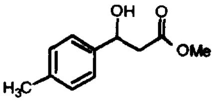
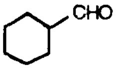
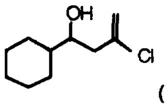
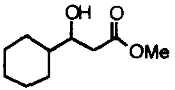
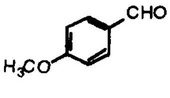
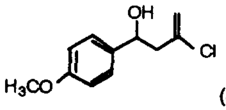
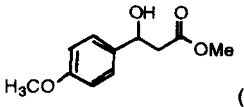
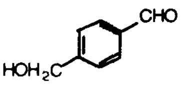
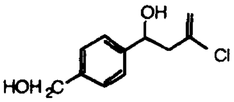
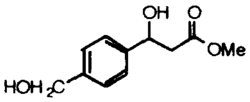
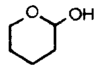
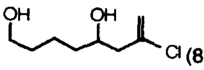
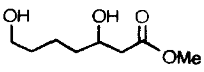
Thus, stirring benzaldehyde with 3-bromo-2-chloro-1-propene and indium in water gave the corresponding allylation product. ^{1}H NMR measurement of the crude product indicated, virtually, a quantitative reaction. Isolation with chramotography provided 78% of the allylation product **4**. Upon ozonolysis, compound **4** was converted to the corresponding β-hydroxyl methyl ester in 82% yield (Entry 1). Other aldehydes reacted similarly, and the results are summarized in Table 1. Attachment of various functionalities on the aromatic ring provides an equivalent or better overall yields of the product (Entries 2, 4, 5 and 7). Aliphatic aldehydes were similarly transformed to the corresponding β-hydroxyl esters (Entries 3 and 6). The use of a mixture of water and THF as solvent for the indium mediated allylation did not affect the reaction result (Entry 4). It is noteworth to mention that compounds with a free hydroxyl group (entry 8) can be converted directly to the corresponding β-hydroxyl ester. In entry 9, eventhough the aldehyde existed in its cyclized hemiacetal form, the compound was transformed to the desired compound without any difficulty.

In conclusion, we have derived an effective and alternative method for the preparation of β-hydroxyl esters. The overall reaction is equivalent to a direct Reformatsky reaction in water. The methyl group of the ester could be changed very easily to others simply by switching the solvent for ozonolysis. Hydroxylated compounds can be transformed to their β-hydroxyl esters directly. The potential application of the present β-hydroxyl ester synthesis are under investigation.

A typical experimental procedure is as following:

To a suspension of p-tolualdehyde (241 mg, 2.0 mmol), 3-bromo-2-chloro-1-propene (633 mg, 4.05 mmol) in 2.4 mL of water was added indium powder (487 mg, 4.2 mmol). The mixture was stirred vigorously at room temperature for overnight under an atmosphere of air, followed by quenching the reaction with 4 mL 1 N HCl aqueous solution. The reaction mixture was extracted with ether (3x10 mL). The combined ethereal layer was washed with saturated $NaHCO_3$ aqueous solution and brine, dried over sodium sulfate, filtered and concentrated to give a crude alkylation product.

Table 1: Preparation of β-hydroxyl Ester by Indium Mediated Reactions in Water

Entry	RCHO(1)	Equiv. 3/In	Product (Yield%) (4)	Product (Yield%) (5)
1		1.6/2.0^a	 (78)	 (82)
2		1.7/2.1^a	 (91)	 (67)
3		2.0/2.0^a	 (58)	 (83)
4		2.0/2.0^b	 (82)	 (99)
5		2.0/2.1^a	 (91)	 (97)
6		1.7/2.3^a	 (77)	 (71)
7		2.6/2.4^a	 (84)	 (81)
8		2.4/2.1^b	 (97)	 (64)
9		3.1/2.6^c	 (84)	 (54)

Allylation of all carbonyl compounds with 3-bromo-2-chloro-1-propene and indium were carried out at room temperature, solvent: a: H_2O; b: THF/H_2O (1:3); c: 0.01 N HCl.

The above crude mixture was then dissolved in 15 mL of methanol. The solution was cooled to -78°C and bubbled with ozone for 30 min till the appearence of blue color. The excess ozone in the solution was then driven out by flushed with oxygen gas. Sodium sulfite fine crystal (2.63 g, 18.5 mmol) was then added at -78°C. The mixture was slowly warmed to room temperature and the stirring was continued for overnight. Then the mixture was filtered, and the collected solid was washed with THF. The combined filtrate was concentrated. The desired β-hydroxyl ester (345 mg, 88% over two steps) was isolated by passing through a short pad of silica gel with ether as the eluent. The product was essentially pure as shown by both TLC and ^{1}H NMR.

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