A Facile and Direct Synthesis of γ -Lactones from Methyl β -Bromopropionate and Ketones mediated by Lanthanoid Metals

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 γ -Lactones were easily prepared from the direct reaction of methyl β -bromopropionate with ketones mediated by lanthanoid metals; a lanthanoid metal ester homoenolate (β -lanthanoid metal substituted ester) is postulated as a reaction intermediate.

In recent years, the chemistry of metal homoenolates (β -metal substituted carbonyl compounds) has advanced leading to the design of several synthetic equivalents¹ and several studies on their use in synthesis.² Among them, β -metallo ester (1) is considered to be an important intermediate in the preparation of γ -lactones from the reaction with ketones and aldehydes. Kuwajima et al. reported the preparation of (1) from 1-alkoxy-1-trimethylsiloxycyclopropane (2) and various metal halides.³ However, a preferable route to (1) is via direct reaction between a metal and the corresponding β -halogeno ester such as β -bromopropionic esters (3). To our knowledge, only one example is known of the direct synthesis of lithium β -lithiopropionate (1; M = R = Li) from β -bromopropionic acid (3; R = H) and organolithium compounds.⁴ We now report that when lanthanoid metals (Ln) are used, y-lactones are obtained in reasonable yields from the direct reaction of (3) with ketones in tetrahydrofuran (THF) under mild conditions,⁵ whereas metals such as zinc and magnesium hardly produce any reaction.

Initially, we were not certain that lanthanoid metals would react with (3) since their inactivity toward alkyl bromide has been reported.⁶ However, on treatment with a trace of iodine the reaction proceeded smoothly, accompanied by a slight temperature rise. When ketone (5) was added to the resulting mixture thought to contain the lanthanoido ester homoenolate (4) at room temperature, an additional exothermic reaction occurred, during which period a fine black precipitate was formed. The major product of the reaction was always the γ -lactone (6), but in some cases there was some contamination with the pinacol coupled product (7) (Scheme 1).† The results are given in Table 1 for the lanthanoid metals, lanthanum, cerium, neodymium, and samarium. There was little difference between the lanthanoid metals used, the yields of the y-lactone from acetophenone being almost the same (70%)(entry 1). From linear, cyclic, and aromatic ketones, the products (6) were produced in moderate to good yields (entries 2---6). In the case of aldehydes such as benzaldehyde and isobutyraldehyde, unfortunately y-lactones were hardly obtained under these conditions, giving a mixture of several unidentified products. From the olefinic ketone hex-5-en-2one, the olefinic γ -lactone derivative was obtained without any side reactions (entry 7), when the olefin group may then be converted into other functional groups.

On the other hand, the use of magnesium and zinc instead of a lanthanoid metal hardly afforded the γ -lactones even under



[†] The pinacol coupling may be induced by a lanthanoid hydride species such as HLnBr which is formed through a β -hydrogen elimination.⁷ The formation of acrylic acid ester was in fact detected.

ultrasonic irradiation or on heating, leading instead to the recovery of the unreacted metals and the starting organic compounds. Therefore, this direct method for γ -lactone preparation is unique for a lanthanoid element.

The following provides a typical procedure using acetophenone and cerium as the ketone and lanthanoid components, respectively. Under a nitrogen atmosphere, the bromoester (**3**; R = Me) (0.67 g, 4 mmol) in THF (2 ml) was added to cerium powder (0.56 g, 4 mmol) and a trace of iodine. The mild exothermic reaction started in a few minutes, then acetophenone (0.48 g, 4 mmol) in 3 ml of THF was injected into the solution. The mild exothermic reaction continued and additional THF (5 ml) was introduced. The resulting solution was stirred at room temperature for 2 h, during which period a fine black precipitate was formed. The mixture was worked up in the usual manner, and the products were analysed by g.l.c. The resulting γ -lactone (**6**; R¹ = Ph, R² = Me, 0.49 g, 2.8 mmol, 70%) was isolated by flash column chromatography on silica gel eluted by hexane-ether (1:1).

Table 1. Reaction of ketones (5) with methyl β -bromopropionate (3; R = Me) mediated by lanthanoid metals.^a

	Ketone (5)		Product(s).	% vield ^b
Entry	R ¹	\mathbb{R}^2	(6)	(7)
1	Ph	Me	68—71°	1820 ^d
2	Ph	Ph	46e	
3	Et	Et	51e	
4	$C_{6}H_{13}$	Me	61e	20 ^d
5	-[CH ₂] ₄ -		60e	15ª
6	-[CH ₂] ₅ -		55e	32ª
7	$CH_2=CH-[C\dot{H}_2]_2$	Me	69e	

^a (3) (4 mmol), ketone (4 mmol), Ln (4 mmol), THF (10 ml); the reaction was carried out at room temperature for 2 h. ^b Isolated yield. ^c La, Ce, Nd, and Sm were employed as Ln. ^d Determined by g.l.c. ^e Ce was used as Ln.



Scheme 1

We tentatively postulate that the reaction intermediate is a lanthanoid ester homoenolate (4), but this has not yet been confirmed.

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