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Titanocene(III) chloride mediated radical-induced one-pot synthesis of α-methylene-γ-butyrolactones

Moumita Paira, Biplab Banerjee, Samaresh Jana, Samir Kumar Mandal and Subhas Chandra Roy*

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata 700 032, India

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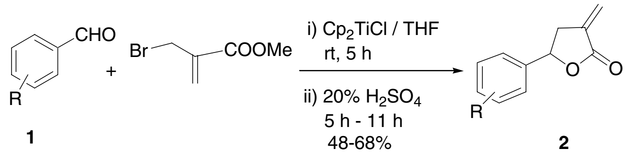
Abstract—A simple and efficient methodology has been developed for the one-pot preparation of α-methylene-γ-butyrolactones by free-radical induced Barbier-type reaction of methyl 2-(bromomethyl)acrylate and aldehydes followed by in situ lactonization. The radical initiator titanocene(III) chloride (Cp_2TiCl) was easily generated in situ from commercially available Cp_2TiCl_2 and activated zinc dust in THF. Ketones remained unaffected under the reaction conditions.

α-Methylene-γ-butyrolactones are versatile structural units present in various important natural products which exhibit interesting biological activities such as antibacterial, anticancer, antimalarial, inhibition of microbial and plant growth, and both convulsant and anti-convulsant activity.[1] Due to their widespread occurrence in nature and broad range of biological activities, much attention has been devoted to the synthesis of α-methylene-γ-butyrolactones. Several methods are available for the introduction of an *exo*-methylene unit into a γ-lactone ring,[2] and for organometal-mediated nucleophilic 2-carboalkoxyallylation of carbonyl compounds.[3] In continuation of our studies[4] towards radical-promoted carbon–carbon bond formation reactions, we have developed a mild and efficient method for the one-pot synthesis of α-methylene-γ-butyrolactones using the Ti(III)-mediated 2-carbomethoxyallylation of aldehydes followed by treatment with aqueous 20% H_2SO_4 which promoted in situ lactonization (Scheme 1). The radical initiator Cp_2TiCl was easily generated in situ from commercially available Cp_2TiCl_2 and activated Zn dust in THF.[5] Although several efficient methodologies are reported in the lit.,[3] the present methodology is comparable in terms of mildness, simplicity and product yields.



Scheme 1.

Thus a series of aldehydes was treated with methyl 2-(bromomethyl)acrylate in the presence of Cp_2TiCl and the results are summarized in Table 1. Aromatic aldehydes **1a**–**j**, aliphatic aldehydes **1k**, **m** and conjugated aldehyde **1l** reacted smoothly to give the corresponding lactones **2a**–**m** in moderate to good yields.[6] All the products were characterized by IR, NMR and HRMS and were compared with authentic samples.[3e–j] Sensitive functionalities such as chloro, allylic and propargylic groups remained unaffected under the reaction conditions. In the case of α,β-unsaturated aldehyde **1l**, the reaction proceeded exclusively via a 1,2-addition producing lactone **2l** in good yield. Reaction of methyl 2-(bromomethyl)acrylate with allyl and propargyl protected salicylaldehydes **1h** and **1i** furnished the expected lactones **2h** and **2i**, respectively, without any intramolecular cyclization as previously observed in our laboratory.[7] This is probably due to the fact that the formation of radicals from methyl 2-(bromomethyl)-acrylate is much faster compared to the aldehydes. It is noteworthy that under the reaction conditions, ketones such as acetophenone and cyclohexanone did

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Keywords: Titanocene(III) chloride; Radical reaction; α-Methylene-γ-butyrolactones.

* Corresponding author. Tel.: +91 33 2473 4971; fax: +91 33 2473 2805; e-mail: ocscr@iacs.res.in

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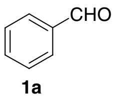
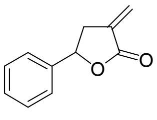
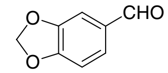
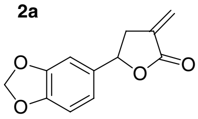
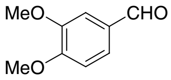
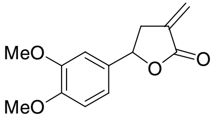
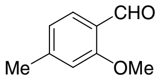
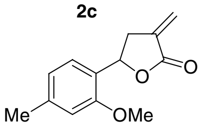
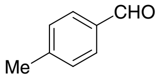
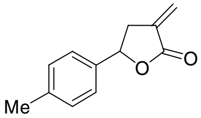
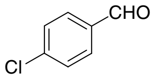
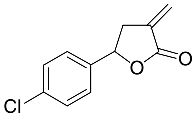
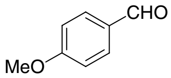
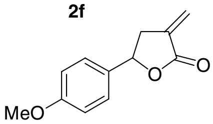
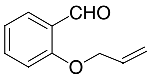
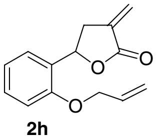
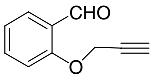
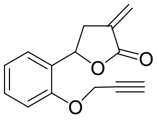
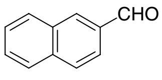
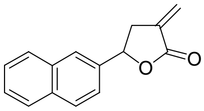
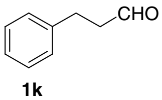
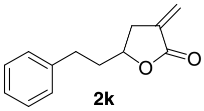
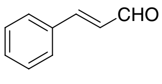
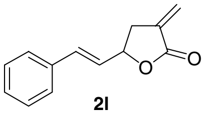
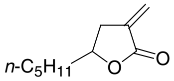
Table 1. Cp_2TiCl Mediated synthesis of α-methylene-γ-butyrolactones

Entry	Substrate	Product	Time (h)	Yield[a] (%)
1	 **1a**	 **2a**	12	64
2	 **1b**	 **2b**	16	62
3	 **1c**	 **2c**	14	61
4	 **1d**	 **2d**	10	68
5	 **1e**	 **2e**	12	52
6	 **1f**	 **2f**	15	48
7	 **1g**	 **2g**	14	60
8	 **1h**	 **2h**	12	62
9	 **1i**	 **2i**	13	66
10	 **1j**	 **2j**	12	59
11	 **1k**	 **2k**	16	51
12	 **1l**	 **2l**	10	63
13	n-$C_5H_{11}CHO$ **1m**	 **2m**	15	67

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[a] Yield refers to pure isolated product.

not undergo lactone formation, but instead self-coupling products of methyl 2-(bromomethyl)acrylate were generated by radical-induced dimerization.

In conclusion, we have developed a mild and efficient methodology for the preparation of synthetically important substituted α-methylene-γ-butyrolactones in satisfactory yields via titanocene(III) chloride promoted radical Barbier-type reaction of methyl 2-(bromomethyl)acrylate and aldehydes followed by in situ lactonization.

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6. *Representative procedure*: A solution of titanocene dichloride (249 mg, 1 mmol) in dry deoxygenated THF (10 mL) was stirred with activated zinc dust (196 mg, 3 mmol) (activated zinc dust was prepared by washing 20 g of commercially available zinc dust with 60 mL of 4 N HCl followed by thorough washing with water until the washings became neutral and finally washing with dry acetone and then drying in vacuo) for 1 h under argon. The resulting green solution was added dropwise to a stirred solution of aldehyde **1i** (80 mg, 0.5 mmol) and methyl 2-(bromomethyl)acrylate (90 mg, 0.5 mmol) in dry THF (5 mL) over 1 h at room temperature under argon. The reaction mixture was further stirred for an additional 4 h and then decomposed by stirring with 20% aqueous H_2SO_4 (15 mL) for 11 h. Most of the THF was removed under reduced pressure and the residue obtained was extracted with diethyl ether (4×25 mL). The combined ether layer was successively washed with aqueous $NaHCO_3$ (2×15 mL), water (2×10 mL), brine (10 mL) and finally dried (Na_2SO_4). After removal of the solvent under reduced pressure, the crude residue obtained was purified by column chromatography over silica gel (10% ethyl acetate in petroleum ether) to afford lactone **2i** (76 mg, 66%) as a viscous oil. IR (neat): 1764, 1604, 1492, 1249, 1224, 1130, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.45 (t, $J = 2.1$ Hz, 1H), 2.72–2.79 (m, 1H), 3.37 (ddt, $J = 17.3$, 8.3, 2.4 Hz, 1H), 4.65 (d, $J = 2.2$ Hz, 2H), 5.55 (t, $J = 2.3$ Hz, 1H), 5.67 (dd, $J = 8.1$, 6.0 Hz, 1H), 6.19 (t, $J = 2.6$ Hz, 1H), 6.90–6.94 (m, 2H), 7.20–7.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 35.6, 56.3, 75.0, 76.3, 78.5, 112.4, 122.0, 122.4, 126.4, 129.5, 129.7, 135.0, 154.4, 171.0; HRMS calcd for $C_{14}H_{12}O_3Na$ $[M+Na]^+$ 251.0684. Found: 251.0623.
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