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Indium-promoted Preparation of Substituted α-Methylene-γ-lactones from 2-(Bromomethyl)acrylic Acid and Carbonyl Compounds

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Abstract: The reaction of 2-(bromomethyl)acrylic acid (**1**) with different carbonyl compounds (**2**) [CH_2O, (*E*)-CH_3CH=$CHCHO$, Pr^iCHO, Bu^tCHO, $PhCHO$, $CH_3(CH_2)_5CHO$, *c*-$C_6H_{11}CHO$, Ph_2CHCHO, $(CH_2)_5CO$] and indium powder in a 1:1 THF:H_2O mixture at room temperature affords, after acidic work-up with hydrochloric acid, the corresponding α-methylene-γ-butyrolactones **3**.

The α-methylene-γ-butyrolactone structural unit has been suggested to play an important role in the mechanism of action of many physiologically active compounds.[1] In fact, it is considered that around 10% of the described natural products contain this moiety, mainly in the field of sesquiterpene lactones, and these compounds exhibit interesting biological properties.[2] Among the different methodologies to prepare α-methylene- γ-butyrolactones the procedures using methallylic derivatives, carbonyl compounds and a metal are especially useful, because they avoid the use of a multistep process. Thus, Reformatsky-type reactions using zinc,[3] tin[4] or chromium[5] have been successfully employed starting from the corresponding methacrylic bromides in a one-pot process with carbonyl compounds.[6,7] On the other hand, in the last few years, reports have appeared in the literature using indium metal to promote allylation of carbonyl compounds,[8] one important advantage of this reaction being that it is possible to work both under aqueous and non-aqueous reaction conditions. In this paper we describe a new methodology for the one-pot preparation of α-methylene-γ-butyrolactones promoted by commercially available indium metal under aqueous conditions, starting from 2-(bromomethyl)acrylic acid and carbonyl compounds.

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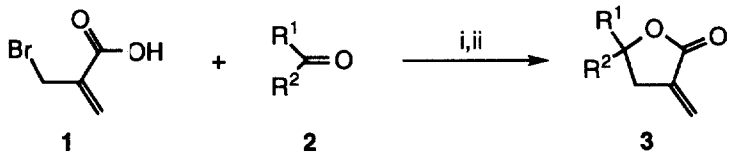
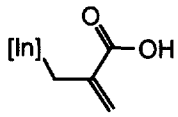
The reaction of 2-(bromomethyl)acrylic acid (**1**) with different carbonyl compounds (**2**) [CH_2O, (*E*)-$CH_3CH{=}CHCHO$, Pr^iCHO, Bu^tCHO, PhCHO, $CH_3(CH_2)_5CHO$, *c*-$C_6H_{11}CHO$, Ph_2CHCHO, $(CH_2)_5CO$) and indium powder (1:2:1:2 molar ratio) in a 1:1 tetrahydrofuran:water solution at room temperature led, after hydrolysis with aqueous hydrochloric acid to the corresponding α-methylene-γ-butyrolactones (**3**), which were purified chromatographically (Scheme 1 and Table 1). In the case of the simplest product **3a**, which is a natural product (tulipalin A),[9] its isolation and purification was carried out by distillation at reduced pressure (Table 1, entry 1). In some cases, it was necessary to prolong the acidic treatment to 3 hours during the work-up in order to get the full conversion to the final lactone, otherwise a mixture of the expected lactone and its hydroxyacid was obtained (Table 1, entries 2, 3 and 6-8). As an example, when the crude reaction mixture using isobutyraldehyde (**2**: R^1 = H, R^2 = Pr^i) was hydrolysed under acidic conditions and worked-up immediately, a 2:1 mixture (GLC) of compound **3c** and 4-hydroxy-5-methyl-2-methylenehexanoic acid[10] was obtained; however, only the expected lactone **3c** was obtained when the same reaction crude was treated with 6 *N* hydrochloric acid for 3 h (Table 1, entry 3).



1 **2** **3**

Scheme 1. *Reagents and conditions*: i, In powder, THF-H_2O, 20°C; ii, HCl-H_2O.

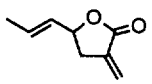
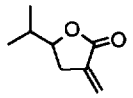
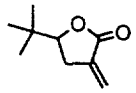
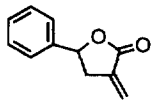
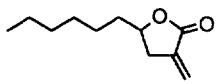
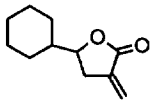
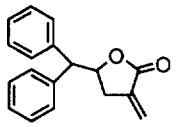
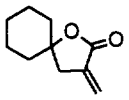
Concerning a possible mechanistic pathway, in other indium promoted allylation reactions,[11] allylindium sesquihalides of type **I** have been proposed to be involved in the process, being prepared, isolated and characterised in many cases. The reaction of this species with the carbonyl compound, followed by cyclisation during the acidic work-up would afford the isolated lactones **3**.



I, [In]: $In_{2/3}Br$

In conclusion, we have described here a simple methodology for the preparation of substituted α-methylene-γ-butyrolactones starting from 2-(bromomethyl)acrylic acid and carbonyl compounds using indium powder as the promoter under aqueous conditions.

Table 1. Preparation of α-Methylene-γ-butyrolactones **3**

Entry	Carbonyl compound	Reaction time (h)	Product[a]			
			Structure	No.	Yield (%)[b]	R_f[c]
1	H_2CO	4.5		**3a**	40[d]	- [e]
2	$CH_3CH{=}CHCHO$	3[f]		**3b**	77	0.37
3	PriCHO	3[f]		**3c**	69	0.41
4	ButCHO	6		**3d**	78	0.48
5	PhCHO	6		**3e**	75	0.29[g]
6	$CH_3(CH_2)_5CHO$	3[f]		**3f**	89	0.43
7	c-$C_6H_{11}CHO$	4[f]		**3g**	90	0.44[h]
8	Ph_2CHCHO	4.5[f]		**3h**	91	0.30[i]
9	$(CH_2)_5CO$	4		**3i**	78	0.42

[a] All isolated products **3** were fully characterised by spectroscopic means (IR, ^1H and ^{13}C NMR and mass spectrometry). [b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting carbonyl compound **2**. [c] Silica gel, hexane/ethyl acetate: 5/1. [d] Isolated yield after distillation at reduced pressure (1 Torr). [e] Bp: 75-77°C/1 Torr (Kugelrohr). [f] The crude reaction mixture was stirred for 3 h with 6N HCl. [g] Mp: 52-54°C (pentane/CH_2Cl_2). [h] Mp: 54-56°C (pentane/CH_2Cl_2). [i] Mp: 119-120°C (pentane/CH_2Cl_2).

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6. When dimetallated methallyl alcohol was used instead of the corresponding acid or ester it was necessary to carry out an oxidation with MnO_2 in order to get the expected α-methylene- γ-butyrolactone. See, for instance: Carlson, R. M. *Tetrahedron Lett.* **1978**, 111-114.
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8. For an excellent review, see: (a) Cintas, P. *Synlett* **1995**, 1087-1096. For recent accounts on indium-promoted allylation of γ-hydroxy-γ-lactones[8b] and acyl chlorides,[8c] see: (b) Bernardelli, P.; Paquette, L. A. *J. Org. Chem.* **1997**, *62*, 8284-8285. (c) Yadav, J. S.; Srinivas, D.; Reddy, G. S.; Bindu, K. H. *Tetrahedron Lett.* **1997**, *38*, 8745-8748.
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