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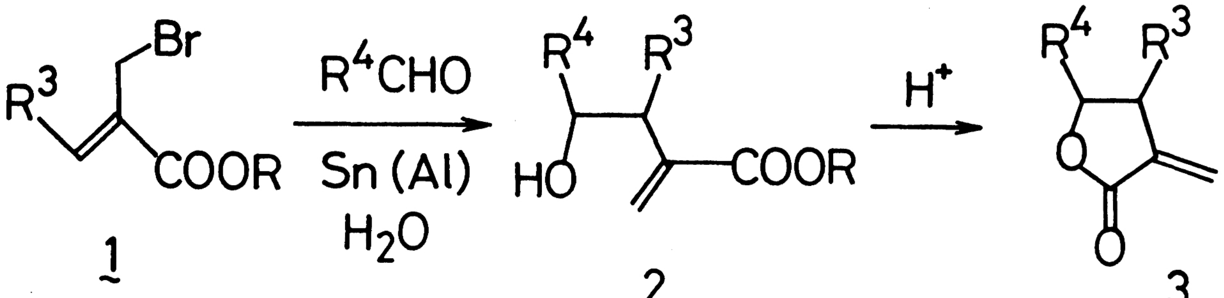
FACILE SYNTHESIS OF 2-METHYLENE-4-BUTYROLACTONES[1)]

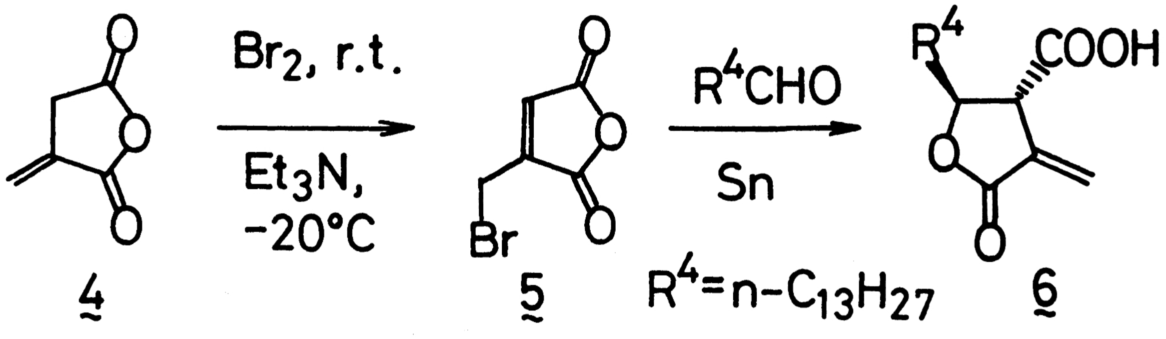
Junzo NOKAMI,* Takashi TAMAOKA, Hideki OGAWA, and Shoji WAKABAYASHI
Okayama University of Science, Ridai, Okayama 700

2-Methylene-4-butyrolactones were conveniently synthesized by treatment of an aldehyde with 2-carboethoxyallyl(-ic) bromide and metallic tin (and aluminum) in good yields. Protolichesterinic acid was synthesized by employing the method.

Many natural compounds having 2-methylene-4-butyrolactone functionality are known to exhibit remarkable biological activities. In the synthesis of those compounds, considerable effort has been devoted to the development of methods for the introduction of the functionality.[2)] Recently, Nozaki et al.[3)] reported a direct method for the preparation of 2-methylene-4-butyrolactones based on 2-carboethoxyallylation of aldehydes[4)] by means of a chromium(II) reagent. Here, we propose that metallic tin[5)] is also effective for direct synthesis of 2-methylene-4-butyrolactones via functionalized-allylation of aldehydes using 2-carboethoxyallyl(-ic) bromides (1).



2-Carboethoxyallyl(-ic) bromides (1a; R^3=H,[6)] 1b; R^3=CH_3, 1c; R^3=C_2H_5, and 1d; R^3=COOEt) were treated with metallic tin (and aluminum) and aldehydes in aqueous and/or in nonaqueous media to give 2-methylene-4-butyrolactones (3) as shown in Table 1. The method was characterized by the following facts: (1) Commercial metallic tin powder (ca. 300 mesh) is useful without any pretreatment for activation. (2) 3,4-Disubstituted 2-methylene-4-butyrolactones are also obtained in satisfactory yields *in the presence of metallic aluminum* (Method A). The geometry of the products from 1b and 1c is cis and that from 1d is trans selectively. (3) The reaction may be successfully carried out in the presence of water in a two phase (ether/water) system.7) The following procedure is typical. To a stirred suspension of metallic tin (2 mmol) in ether (4 ml) and water (1 ml) were added 1a (2 mmol), hexanal (2.2 mmol), and catalytic amount of acetic acid, and the stirring was continued for 9 h with gentle refluxing of ether. Work-up gave a mixture of 2-methylene-4-pentyl-4-butyrolactone (3) and ethyl 4-hydroxy-2-methylenenonanoate (2). The mixture was treated with catalytic amount of p-toluenesulfonic acid in benzene at r.t. to convert 2 to the lactone 3, which was purified by column chromatography on silica gel, in 68% yield based on the bromide 1a. When 1.5 mmol of hexanal was used, the lactone was obtained in 85% yield based on the aldehyde. Also, some larger scale experiments showed satisfactory results. When 2-carboethoxyallylic bromides (1b, 1c, and 1d) were allowed to react with aldehydes to give the corresponding 3-substituted 2-methylene-4-butyrolactones, an additive effect of metallic aluminum was observed not only in the yield of the products, but also in the stereoselectivity of the reaction as shown in Table 1. The method was employed to synthesize protolichesterinic acid8) as shown below.



2-Methylenesuccinic anhydride (4) was treated with bromine in carbon tetrachloride at r.t. for 24 h and followed with triethylamine at -20 °C for 3 h to afford 2-bromomethylmaleic anhydride (5) in 70% yield after column chromatography on silica gel. To a solution of the bromide 5 in 1,2-dimethoxyethane (DME) were added metallic tin and tetradecanal, and the mixture was stirred for 10 h at 40 °C. The crude product was purified by column chromatography on silica gel to give trans protolichesterinic acid (6) in 25% yield and the cis isomer (7) in 8% yield.9)

Table 1. Metallic tin promoted reaction of 2-carboethoxyallyl(-ic) bromides with aldehydes to 2-methylene-4-butyrolactone a)

R^3-CH=$\underset{\text{COOEt}}{\text{C}}$-$CH_2$Br b) R^3=		Aldehyde c)	Solvent d)	Reaction time/h	Lactone 3 Yield/% e)	
					Method A (cis/trans)	Method B (cis/trans)
H	1a	n-C_5H_{11}CHO	aq. THF	9	51	50
			Et_2O-H_2O	9	49	68
			THF	9	62	67
			DMF	7	81	66
		CH_3CH=CHCHO	Et_2O-H_2O	8		75
			DME	10	51	
		C_6H_5CHO	Et_2O-H_2O	10		74
			DME	6	66	
		HCHO f)	Et_2O-H_2O	9		68 g)
		citral	Et_2O-H_2O	8		57
CH_3	1b	n-C_5H_{11}CHO	Et_2O-H_2O	12	62 / 0	62 / 0
			DME	12	66 / 0	
		CH_3CH=CHCHO	Et_2O-H_2O	10	69 / 0	46 / 3
			DME	6	65 / 0	
		C_6H_5CHO	Et_2O-H_2O	9	68 / 0	
			Et_2O-H_2O	16		20 / 22
			DME	8	75 / 0	48 / 0
		HCHO f)	Et_2O-H_2O	10	73	
C_2H_5	1c	n-C_5H_{11}CHO	Et_2O-H_2O	14	54 / 0	
			DME	10	68 / 0	
		CH_3CH=CHCHO	DME	10	65 / 0	
		C_6H_5CHO	Et_2O-H_2O	9	50 / 0	
			DME	12	74 / 0	30 / 16
		HCHO f)	Et_2O-H_2O	12	60	
COOEt	1d	n-C_5H_{11}CHO	THF	3	0 / 70 g)	20 / 51 g)
		CH_3CH=CHCHO	THF	3	0 / 52	6 / 58
		C_6H_5CHO	Et_2O-H_2O	6		0 / 42
			THF	3	0 / 71	10 / 68
			DME	5		0 / 68

a) At 40 °C, ca. 2 mmol scale unless otherwise noted. b) 1a-1c were prepared according to the method reported by Hoffmann et al.6) and 1d was prepared by treatment of diethyl citraconate with N-bromosuccinimide in refluxing carbon tetrachloride for 10 h in 91% yield. c) Commercial aldehyde (2.2 mmol) was used without purification. d) Freshly distilled dry THF and special grade of commercial 1,2-dimethoxyethane (DME) were used. e) Isolated yield; Method A: in the presence of metallic aluminum equimolar with metallic tin. Method B: in the absence of metallic aluminum. f) Formaldehyde, 37 wt. % solution in water. g) 10 mmol scale.

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7) Allyltin compounds produced by the reaction of allyl(-ic) halides with metallic tin (and aluminum) (previously reported)$^{5)}$ were stable in aqueous media and the reaction of the tin compounds with aldehydes and ketones to homoallyl(-ic) alcohol was accelerated in the presence of water. However, allylic tin compounds derived by the reaction of 2-carboethoxyallylic bromides with metallic tin (and aluminum) (presented here) were unstable in homogeneous aqueous media and 1b, 1c, and 1d were reduced to ethyl 2-methylenebutanoate, ethyl 2-methylenepentanoate, and diethyl 2-methylenesuccinate respectively by the reaction with metallic tin in aqueous DME, aqueous THF, alcohol, etc. The reaction in the two phase system gave satisfactory results.

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9) Structural assignment based on the NMR spectrum of the methyl ester of protolichesterinic acid and its cis isomer, see Ref. 4a (Löffler et al.).

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