## NEW SYNTHETIC METHOD OF (Z)-4-ALKENOIC ACIDS USING RING-OPENING REACTION OF (Z)-4-HEXENOLIDE WITH ORGANOCOPPER REAGENT

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(Z)-4-Hexenolide reacted regioselectively with diorganocuprates to give (Z)-4-alkenoic acids in high yields. Synthetic utility was demonstrated by the convenient synthesis of *cis*-jasmone.

(Z)-4-Alkenoic acids are components of perfumes and flavors,<sup>1)</sup> and they can also be utilized as a synthetic block in the synthesis of various natural products.<sup>2)</sup> Although one-pot synthesis of (Z)-4-alkenoic acids was already reported from our laboratory,<sup>3)</sup> here we wish to report further convenient synthetic method for (Z)-4-alkenoic acids by the reaction of (Z)-4-hexenolide with diorganocuprate. In the previously reported reaction of  $\omega$ -alkenyl lactones with organocopper reagent,<sup>5)</sup> the reagent attacked mainly the terminal vinyl carbon of the lactone to result in  $S_N2$ ' type reaction and its regio- and stereoselectivities were influenced by the reaction conditions such as solvent, reaction temperature, and by the structure of lactones. When we tried to prepare  $\gamma$ -vinyl- $\gamma$ -butyrolactone, as the starting material for the synthesis of (E)-4-alkenoic acid according to Birch's method,<sup>4)</sup> *i.e.*, distillation of 2-vinylcyclopropane-1,1-dicarboxylic acid, it was found that obtained products were the mixture of (Z)-4-hexenolide and  $\gamma$ -vinyl- $\gamma$ butyrolactone in the ratio of about 4:6. In this way, (Z)-4-hexenolide came into our notice because it possessed allylic ester structure having Z configuration of carbon-carbon double bond. To our surprise, in the ring-opening reaction of (2)-4hexenolide with diorganocuprate,  $S_N2$  type product of (2)-4-alkenoic acid was obtained predominantly.

(2)-4-Hexenolide (1) was easily prepared by the modified procedure of Birch's method.<sup>6)</sup> To a solution of diorganocuprate prepared from 1.1 equivalent of copper(I) iodide and 2.2 equivalent of alkyllithium or Grignard reagent, was added dropwise a solution of 1. The reaction mixture was stirred at appropriate temperatures. Then usual work-up gave a mixture of 4-alkenoic acid 2,  $S_N 2$  type reaction product, and 4-substituted 5-hexenoic acid 3,  $S_N 2$ ' type reaction product.



Entry	R <sup>2</sup> CuM	Solvent	Temp °C	<u>Time</u> min	Yield/% 2 + 3	Product $(Z)-2:(E)-2$	ratio <sup>c)</sup> 2 :	3
1	(CH <sub>3</sub> ) <sub>2</sub> CuLi	Et <sub>2</sub> O	0	30	90	98:2	88 : ]	12
2	(CH <sub>3</sub> ) <sub>2</sub> CuLi	Et <sub>2</sub> O	-30	60	23 <sup>d)</sup>	93 <b>:</b> 7	85 <b>:</b> ]	L5
3	(CH <sub>3</sub> ) <sub>2</sub> CuLi	THF	0	30	92	58 : 42	90 <b>:</b> ]	LO
4	(CH <sub>3</sub> ) <sub>2</sub> CuMgBr	THF-Me <sub>2</sub> S	-30	60	67	76 <b>:</b> 24	92 <b>:</b>	8
5	(CH <sub>3</sub> ) <sub>3</sub> CuLi <sub>2</sub>	$Et_2O$	0	30	89	>99 : <1	85 <b>:</b> 1	L5
6	(CH <sub>3</sub> ) <sub>2</sub> Cu(CN)Li <sub>2</sub>	THF	0	30	40	>99 : <1	97 <b>:</b>	3
7	(C <sub>4</sub> H <sub>9</sub> ) <sub>2</sub> CuLi	Et <sub>2</sub> O	0	30	92	>99 : <1	86 <b>:</b> ]	L4
8	(C <sub>4</sub> H <sub>9</sub> ) <sub>2</sub> CuMgBr	THF-Me <sub>2</sub> S	-30	30	84	97:3	94 :	6
9	(C <sub>5</sub> H <sub>11</sub> ) <sub>2</sub> CuLi	$Et_2O$	0	30	84	>99 : <1	86 <b>:</b> ]	L4
10	(C <sub>6</sub> H <sub>13</sub> ) <sub>2</sub> CuLi	Et₂O	0	30	85	>99 : <1	86 <b>:</b> ]	L4
11	(s-C4H9)2CuLi <sup>b)</sup>	THF	0	30	20	65 : 35	75 <b>:</b> 2	25
12	(s-C4H9)2CuMgCl	THF-Me <sub>2</sub> S	-30	30	84	>99 : <1	94 :	6
13	$(t-C_{4}H_{9})_{2}CuLi^{b})$	THF	0	30	0	—		
14	$(t-C_4H_9)_2$ CuMgCl	THF-Me <sub>2</sub> S	-30	30	80	95 <b>:</b> 5	90 <b>:</b> 1	L0
15	$(C_6H_5)_2$ CuLi	Et <sub>2</sub> O	0	30	84	99 : 1	84 <b>:</b> 1	16

Table 1. Reaction of Diorganocuprates with (Z)-4-Hexenolide<sup>a)</sup>

a) All reactions were carried out on 1 mmol scales with same procedure as described in the text.
All products were identified by IR and NMR spectra.
b) These cuprates are not stable at 0 °C in ether: see Ref. 7.
c) The ratios were determined by a capillary GLPC analysis (SE-30, 50 m).
d) By-products were 7-hydroxy-(Z)-5-hepten-2-one (35%) and 6-methyl-(Z)-2-heptene-1,6-diol (20%).

Table shows the results obtained in the reaction of representative diorganocuprates with (Z)-4-hexenolide. In the use of lithium dimethylcuprate, ether was better as solvent than THF with regard to regio- and stereoselectivities (entries 1 and 3). Low reaction temperature caused the decrease of the yield along with lowering of regio- and stereoselectivities (entry 2). Dilithium dimethylcyanocuprate showed best regio- and stereoselectivities but unfortunately the yield was low (entry 6). Halomagnesium dialkylcuprates can not be prepared in ether because of its insolubility and instability, and they gave higher regioselectivity but lower stereoselectivity than lithium dialkylcuprates. Further this ring-opening reaction of (Z)-4-hexenolide was applicable for aryl cuprate to afford the corresponding (Z)-4-alkenoic acid in good yield (entry 15). It is noteworthy that (Z)-4hexenolide reacted with dialkyl cuprate selectively in a  $S_{\rm N}2$  fashion, although the reaction of allylic esters such as  $\omega$ -vinyl lactones with organocopper reagent gives generally  $S_N2'$  type products.<sup>5)</sup> The  $S_N2$  product, 4-alkenoic acid 2, could be separated from 4-substituted 5-hexenoic acid 3 by purification of the corresponding benzyl ester by a column chromatography.

A representative procedure for the synthesis of 4-heptenoic acid is as follows. A solution of (Z)-4-hexenolide (401 mg, 3.58 mmol) in Et<sub>2</sub>O (2 ml) was added to a solution of lithium dimethylcuprate prepared from 0.876 M ether solution

of methyllithium (9.20 ml, 8.06 mmol) and copper(I) iodide (768 mg, 4.03 mmol) in ether (16 ml) at 0 °C. The reaction mixture was stirred at the same temperature for 30 min, quenched with 2 M hydrochloric acid, and extracted with ether. Ether solution was washed with 3 M aqueous NaOH. After the aqueous alkaline solution was acidified with 6 M hydrochloric acid and extracted with ether, evaporation of the solvent gave a crude acid. Bulb to bulb distillation furnished a mixture of 4-heptenoic acid (4) and 4-methyl-5-hexenoic acid (413 mg, 3.22 mmol) in 90% yield. Then the mixture was esterified (84%) by refluxing with benzyl alcohol in benzene in the presence of *p*-toluenesulfonic acid for 4 h and benzyl 4-heptenoate was separated by silica gel column chromatography (hexane:Et<sub>2</sub>O = 200:1) in 72% recovery. After hydrolysis of the ester in alcoholic KOH at room temperature for 1 h, pure 4-heptenoic acid was obtained in 95% yield.

Utilizing this regioselective ring-opening reaction of (Z)-4-hexenolide with lithium dimethylcuprate, *cis*-jasmone can be conveniently synthesized in short steps. Reaction with 3,3-ethylenedioxybutylmagnesium chloride in the presence of 5 mol% copper(I) iodide using l-chloro-2-methyl-N,N-tetramethylenepropenylamine as a condensation agent<sup>8)</sup> to produce the ketone (5) in 91% yield. After hydrolysis of acetal by stirring in acetone in the presence of catalytic amount of 2 M hydrochloric acid at room temperature, cyclization of the diketone with alcoholic KOH according to the usual method<sup>2)</sup> gave *cis*-jasmone (6) in 79% yield (*E*:*Z* = 98:2).



As described above, this new synthetic method of (Z)-4-hexenoic acid has the following advantages, i) easy availability of the starting material, (Z)-4-hexenolide, ii) simple procedure and mild conditions, and iii) good yields accompanied with high selectivites.

## References

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- 6) (Z)-4-Hexenolide was easily prepared by the following procedure: To a solution of sodium methoxide prepared from sodium (7.6 g, 330 mg-atom) in methanol (150 ml), was added dropwise a solution of dimethyl malonate (20.7 g, 157 mmol) in methanol (10 ml) at room temperature over 15 min. After stirring the resulted white suspension at the same temperature for 30 min, a solution of trans-1,4dichloro-2-butene (21.6 g, 173 mmol) in methanol (10 ml) was added at once to the vigorously stirred suspension. Immediately, exothermic reaction occurred and the reaction mixture was further stirred at 50 °C for 3 h after evolution of heat ceased. Removal of the precipitate by the filtration through a Celite pad, evaporation of the solvent and distillation gave 1,1-bis(methoxycarbony1)-2vinylcyclopropane (24.6 g, 134 mmol) in 85% yield. The ester was hydrolyzed in usual way to produce dicarboxylic acid. Distillation of the acid accompanied with decarboxylation gave a mixture of  $\gamma$ -vinyl- $\gamma$ -butyrolactone (28%) and (Z)-4hexenolide (20%), which were easily separable by preparative open column chromatography (silica gel). (Z)-4-Hexenolide: NMR (CCl<sub>4</sub>)  $\delta$  2.5 (2H, m, CH<sub>2</sub>CO), 2.8 (2H, m, CH<sub>2</sub>CH<sub>2</sub>CO), 4.6 (2H, m, CH<sub>2</sub>OCO), and 5.8 (2H, m, CH=CH); IR (neat) 1730 cm<sup>-1</sup> (C=O). Anal. Calcd for  $C_6H_8O_2$ : C, 64.27; H, 7.19%. Found: C, 64.45; Н, 6.92%.
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