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A CONVENIENT METHOD FOR THE SYNTHESIS OF 4-CHLORO-3-ALKENOIC ACID. A NEW USEFUL SYNTHETIC BLOCK FOR 4-OXOALKANOIC AND 4-OXO-2-ALKENOIC ACIDS

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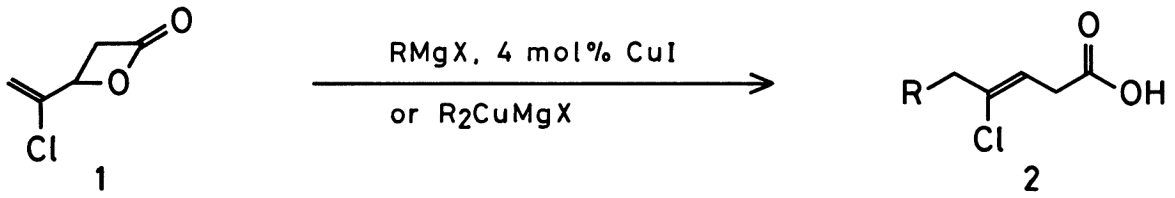
Easily available material, β-(1-chlorovinyl)-β-propiolactone reacted with organocopper reagents to afford 4-chloro-3-alkenoic acids in high yields. The acids were easily transformed into two kinds of useful carboxylic acids such as 4-oxoalkanoic and 4-oxo-(*E*)-2-alkenoic acids leading to various natural products.

Although two methods have been already developed for the synthesis of 4-chloro-3-alkenoic acids,[1] the synthesized acids were only two and the methods have a limit of applicability. 4-Chloro-3-alkenoic acids, however, are very useful synthetic blocks because the acids have noticeable chemical structures such as vinyl chloride and β,γ-unsaturated carboxylic acid. We have already reported the synthetic method of 3-alkenoic acids by the reaction of β-vinyl-β-propiolactone with organocopper reagents.[2] If β-(1-chlorovinyl)-β-propiolactone (1) reacts with organocopper reagent as the case of β-vinyl-β-propiolactone, 4-chloro-3-alkenoic acids (2) are expected to be produced. Here we wish to report a facile synthetic method of 4-chloro-3-alkenoic acids utilizing the regioselective ring-opening reaction of β-(1-chlorovinyl)-β-propiolactone with organocopper reagents and convenient transformation of 4-chloro-3-alkenoic acids to the other important oxocarboxylic acids.

The starting material, β-(1-chlorovinyl)-β-propiolactone (1) was easily prepared[3] by the cycloaddition of ketene with α-chloroacrolein.[4] When the lactone was treated with various kinds of Grignard reagents in the presence of 4 mol% of cuprous iodide in THF-Me_2S (20:1) at -78 °C for 50 min, only S_N2' products, 4-chloro-3-alkenoic acids (2) were formed in high yields. As the substituents of



1 2

Grignard reagents, not only primary, secondary, and tertiary alkyl groups, but also phenyl and vinyl groups could be used. On the other hand, the reaction using diphenyl-, divinyl-, and diallylcuprate gave the corresponding acids 2 in much higher yields than the use of Grignard reagents. Stereochemistry of the newly formed carbon-carbon double bond of the obtained 4-chloro-3-alkenoic acid was determined to be predominant *Z* configuration in all cases, by comparison with ^1H

Table 1. Yields of 4-Chloro-3-alkenoic Acids by the Reaction of β-(1-Chlorovinyl)-β-propiolactone with Organocopper Reagents

		Me	Bu	*s*-Bu	*t*-Bu	Ph		
$RMgX^{a)}$ 4 mol% CuI	Yield/%	81	81	85	76	73	51	25
	E : Z[c)]	93: 7	89:11	85:15	80:20	83:17	95: 5	92: 8
$R_2CuMgX^{b)}$	Yield/%	80	85	91	80	92	71	77
	E : Z[c)]	90:10	89:11	86:14	86:14	84:16	91: 9	91: 9

a) All reactions were carried out on 2 mmol scales with same procedure as described in the text. All products were identified by IR and NMR spectra. b) All reactions were carried out on 2 mmol scales in THF-Me_2S (10:1) at -50 °C for 50 min. c) The ratios were determined by a capillary glpc analysis (SE-30, 50 m).

NMR spectrum data of the analogous compounds[1a)] and capillary glpc analysis (SE-30, 50 m). These results are summarized in Table 1.

The utility of 4-chloro-3-alkenoic acids was next demonstrated by the transformation of the acids 2 to 4-oxoalkanoic acids (3), which are well known as important precursors for γ-substituted-γ-butyrolactones, ubiquitous natural products[5)] in peach, apricot, strawberry, tobacco, *etc.*, *via* γ-hydroxycarboxylic acids.[6)] Although 4-chloro-3-alkenoic acids are hydrolyzed with conc. H_2SO_4[1b)] or methanolic KOH[7)] to give 4-oxoalkanoic acids, the yields of the acids were not so high. Our method was performed according to Mukaiyama's method[8)] of the hydrolysis of vinyl chlorides to ketones. When 4-chloro-3-nonenoic acid was stirred at room temperature for 64 h in a solution of $TiCl_4$ (5 equiv.), MeOH (2 equiv.), H_2O (2 equiv.), acetone (3 equiv.) in CH_2Cl_2, the desired 4-oxononanoic acid was obtained in 82% yield accompanied with 8% yield of methyl 4-oxononanoate. The other 4-chloro-3-alkenoic acids were also hydrolyzed in the same manner to the corresponding 4-oxoalkanoic acids in good yields except for the cases of chlorodienoic acids such as 4-chloro-3,7-octadienoic acid and 4-chloro-3,6-heptadienoic acid as shown in Table 2.

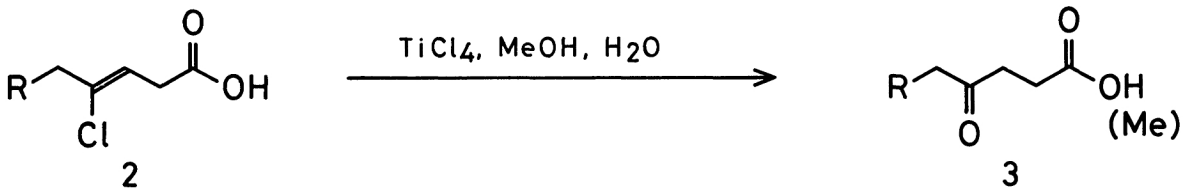


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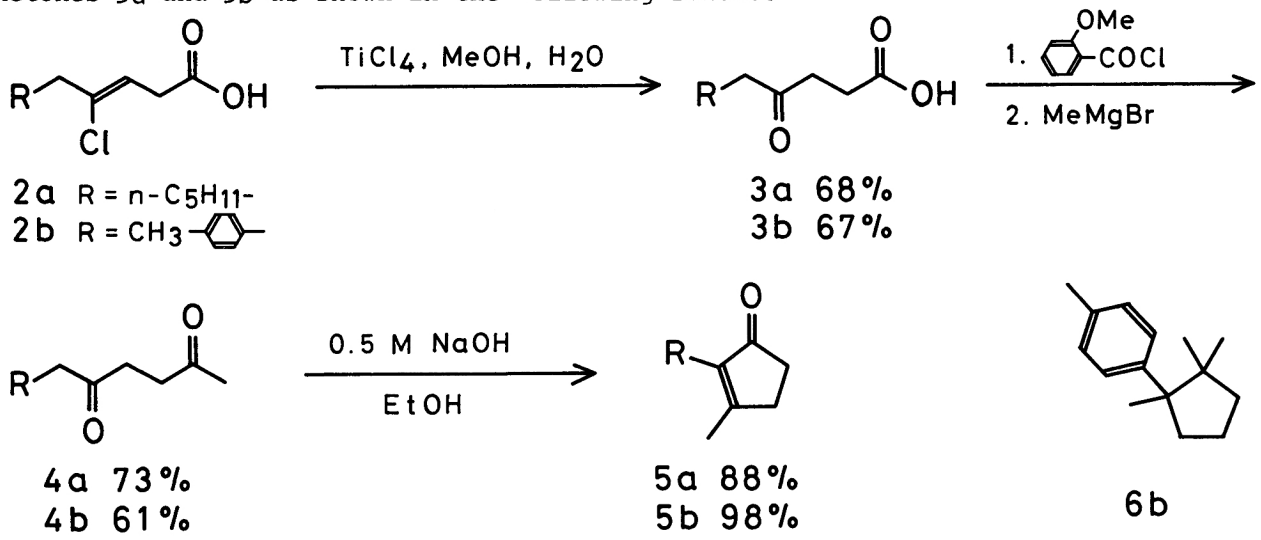
Table 2. Hydrolysis of 4-Chloro-3-alkenoic Acids[a)]

	R	Me	Bu	*s*-Bu	*t*-Bu	Ph		
Yield/%	Acid	66	82	77	71	71	0	5
	Me Ester	10	8	17	23	12	0	0

a) All reactions were carried out on 2 mmol scales with same procedure as described in the text. All products were identified by IR and NMR spectra.

Further, synthetic utility of the present method was shown by short step syntheses of dihydrojasmone (5a) and the precursor 5b of cuparene (6b).[9)] Namely chloroalkenoic acids (2a and 2b) obtained by the reaction of β-(1-chlorovinyl)-β-

propiolactone with di-*n*-pentylcuprate or di-*p*-tolylcuprate were transformed into ketones 5a and 5b as shown in the following scheme.



On the other hand, 4-chloro-3-alkenoic acids (2) were also found to be good synthetic blocks for the synthesis of 4-oxo-(*E*)-2-alkenoic acids (8) *via* 4-hydroxy-(*E*)-2-alkenoic acids (7). In many macrolide antibiotics such as A26771B,[12] pyrenophorin, and vermiculine,[13] 4-oxo-(*E*)-2-alkenoic acids are incorporated. Although many methods have been reported for the preparation of 4-oxo-(*E*)-2-alkenoic acid derivatives[14] satisfactory method have not yet been reported with respect to availability of the starting materials, simplicity of the procedure, yield, and applicability. Our successful method for the synthesis of 4-oxo-(*E*)-2-alkenoic acids (8) was carried out by the hydrolysis of acids 2 by refluxing in aq. NaOH followed by the Jones oxidation. It is noteworthy that the acids 2 gave 4-hydroxy-(*E*)-2-alkenoic acids (7) by refluxing in aq. NaOH, in contrast to the transformation of the acid 2 to 4-oxoalkanoic acid 3 by refluxing in methanolic KOH.[8] When 4-chloro-3-nonenoic acid was refluxed for 20 min in 2 M aqueous solution of NaOH (10 equiv.), 4-hydroxy-(*E*)-2-nonenoic acid was obtained in a yield of 82% accompanied with 8% yield of 2,4-nonadienoic acid. The hydroxy acid was then converted to 4-oxo-(*E*)-2-nonenoic acid by the Jones oxidation at 0 °C for 30 min in a yield of 74%. This procedure was applied to the other 4-chloro-3-alkenoic acids having acid sensitive functional groups such as acetal and tetrahydropyranyl

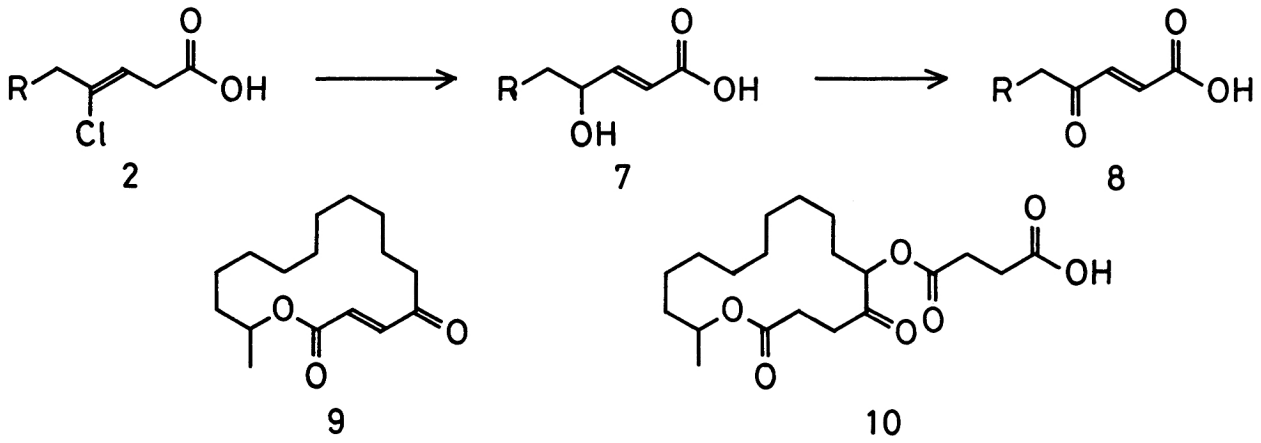
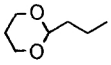


Table 3. The Yields of 4-Chloro-3-alkenoic Acids (2), 4-Hydroxy-2-alkenoic Acids (7) and 4-Oxo-(*E*)-2-alkenoic Acids (8)[a)]

Run	R	2 Yield/%	7 Yield/%	8 Yield/%
c		85	84	74
d		97	62	63
e		86	67	46
f		90		56[b)]

a) All reactions were carried out on 2 mmol scales with same procedure as described in the text. All products were identified by IR and NMR spectra. b) The yield of 15-hydroxy-4-oxo-2-hexadecenoic acid, after acid-catalyzed hydrolysis, calculated from 2f.

group obtained using the corresponding copper reagents to produce 4-oxo-(*E*)-2-alkenoic acids (8) as shown in Table 3. Especially 15-hydroxy-4-oxo-2-hexadecenoic acid (8f) is a precursor of antibiotic A26771B (10). Lactonization of 8f according to the Yamaguchi's method[15)] gave the 16 membered lactone (9) in a yield of 46%. Transformation of 9 to 10 has already been performed by Takei *et al.*[12)]

As described above, reaction of β-(1-chlorovinyl)-β-propiolactone with organocopper reagents afforded 4-chloro-3-alkenoic acids in high yields. The acids are found to be extremely useful building blocks for 4-oxoalkanoic and 4-oxo-(*E*)-2-alkenoic acids leading to various natural products.

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