

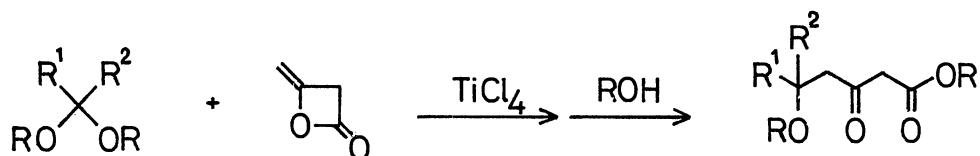
A CONVENIENT METHOD FOR THE PREPARATION OF δ -HYDROXY- β -KETOESTERS AND 6-ALKYL-5,6-DIHYDRO-4-HYDROXY-2-PYRONES. APPLICATION TO THE SYNTHESSES OF KAWAIN AND DIHYDROKAWAIN

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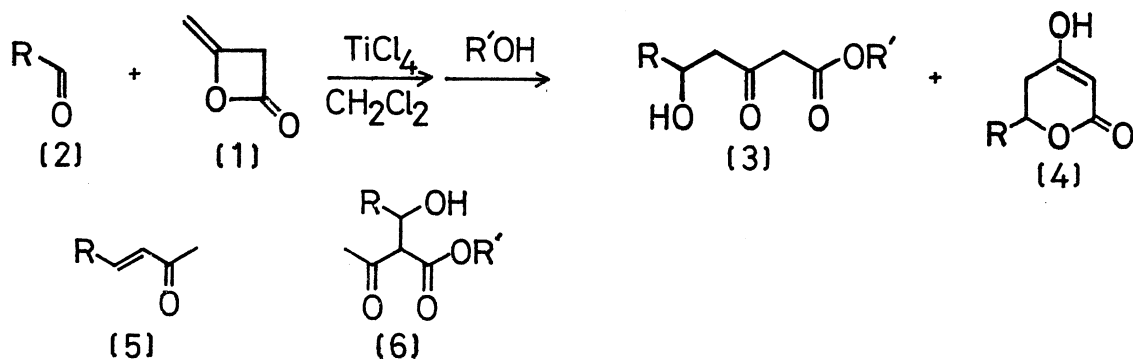
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δ -Hydroxy- β -ketoesters[3] and 6-alkyl-5,6-dihydro-4-hydroxy-2-pyrones[4] were obtained in good yields by TiCl_4 -promoted addition of diketene[1] to various aldehydes[2], followed by the treatment with alcohol. The hydroxyketoesters[3] were easily lactonized to the corresponding lactones[4] in excellent yields by the hydrolysis with aqueous alkali, followed by acidification. The present method was successfully applied to the syntheses of dihydrokawain[7c] and kawain[7d].

During the course of our continuing investigations on the exploration of valuable synthetic reactions by the use of TiCl_4 , it was reported in the previous paper¹⁾ that diketene easily reacts at its exo-double bond with acetals activated by TiCl_4 to form exclusively δ -alkoxy- β -ketoesters in good yields.



In the present experiment, it was established that δ -hydroxy- β -ketoesters[3]²⁾ and 6-alkyl-5,6-dihydro-4-hydroxy-2-pyrones[4] were prepared in good yields by the TiCl_4 -promoted reaction of diketene[1] with various aldehydes[2] at -78°C , followed by the treatment with alcohol($\text{R}'\text{OH}$) as shown in the following scheme.



Concerning the reaction of diketene[1] with aldehydes[2], it has been published³⁾ that α, β -unsaturated ketones[5] were produced accompanying the elimination of carbon dioxide when they were allowed to react under refluxing conditions with or without solvent for a long time. Contrary to the result, the present TiCl_4 -promoted reaction takes place under very mild conditions, resulting in the exclusive formation of δ -hydroxy- β -ketoesters[3] and 6-alkyl-5,6-dihydro-4-hydroxy-2-pyrones[4] without elimination of carbon dioxide after quenching with alcohol. α -(1-Hydroxyalkyl)acetoacetic esters[6] could not be detected.

δ -Hydroxy- β -ketoesters[3] are easily lactonized to the corresponding lactones, 5,6-dihydro-4-hydroxy-2-pyrone derivatives[4], in excellent yields by the treatment with 0.1N-NaOH solution at room temperature for 2hr followed by acidification with 2N-HCl solution.⁵⁾ Lactones[4] are smoothly methylated by dimethyl sulfate at room temperature to afford 5,6-dihydro-4-methoxy-2-pyrones[7].⁷⁾ The results are summarized in Table II.

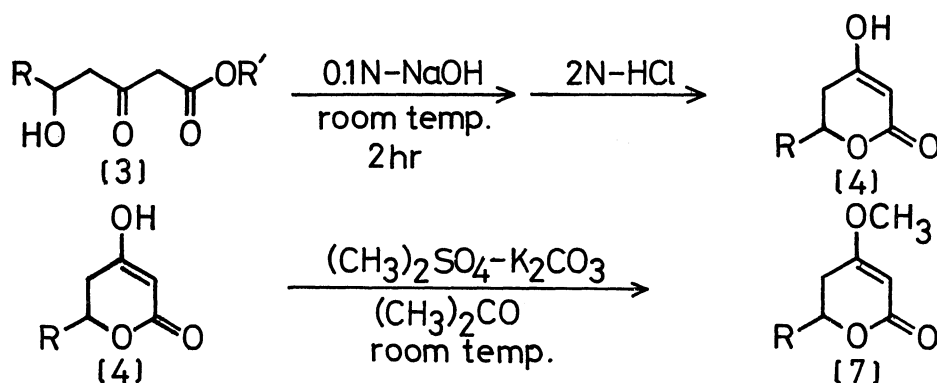





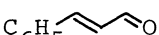
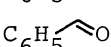


Table II. The Preparation of [4] and [7]

	$\text{R}-\text{CHO}$ [2]	Time ⁱ⁾ (min)	Yield (%)		Yield (%)	
			 [4] ⁱⁱ⁾	Time (hr)	 [7]	
a		60	(78) ⁱⁱⁱ⁾	15	77	
b		5	96	8	84	
c		5	95	20	84	
d		60	47	6	69	
e		5	97	6	84	

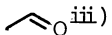
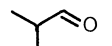

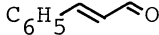
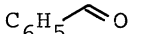
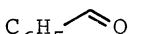

i) The reaction time of diketene[1] with aldehyde[2].

ii) The yields were calculated based on aldehydes[2]. Lactonizations were carried out by treating the reaction mixture, [3] and [4], obtained from diketene[1] and aldehydes[2] (except [2a] and [2d]), with 0.1N-NaOH solution, followed by acidification with 2N-HCl solution.

iii) Yield of the isolated product of the reaction of diketene[1] with paraldehyde as shown in Table I.

A typical experiment is as follows; to a vigorously stirred solution of benzaldehyde[2e] (0.165 g, 1.25 mmol) and diketene[1] (0.5 ml of 5M solution, 2.5 mmol) in dichloromethane (6.5 ml) was injected at once a 3M solution of TiCl_4 (0.5 ml, 1.5 mmol) in dichloromethane at -78°C under an argon atmosphere, and the reaction mixture was stirred for 2 min. Then dry methanol (2 ml) was added to the resulting mixture, and after being stirred for 30 min at $-20 \sim -10^\circ\text{C}$, the mixture was poured into an ice-cooled aqueous K_2CO_3 solution (10 ml, 4.4 mmol). The resulting insoluble pale yellow precipitate was filtered off and the filtrate was extracted twice with ether. The organic layer was washed with saturated NaHCO_3 solution in order to take up lactone[4e] to aqueous layer. The ether extract was washed with saturated brine and the solvent was evaporated. By silica gel column chromatography, methyl 5-hydroxy-3-oxo-5-phenylpentanoate[3e] was isolated in 91% yield (0.253 g). Further, the combined aqueous alkaline solution was evaporated under reduced pressure. The residue was acidified with 2N-HCl solution, extracted well with ethyl acetate and the extract was washed with water and saturated brine. After removal of the solvent, resulting crystalline was washed with small amount of ether, and 5,6-dihydro-4-hydroxy-6-phenyl-2-pyrone[4e] was obtained in 7% yield (0.018 g) (see Table I).

Table I. The Reaction of Diketene[1] with Aldehydes[2] at -78°C

	$\text{R}'\text{CHO}$ [2]	Time (min)	$\text{R}'\text{OH}$ ⁱ⁾	Isolated Yields (%) $\text{R}-\text{CH}(\text{OH})-\text{CH}(\text{O})-\text{CH}_2-\text{CO}-\text{OR}'$ [3] ⁱⁱ⁾	$\text{R}-\text{CH}(\text{OH})-\text{CH}(\text{O})-\text{CH}_2-\text{CO}-\text{O}-\text{R}$ [4] ⁱⁱ⁾
a	 ⁱⁱⁱ⁾	60	CH_3OH	3	78
b		5	CH_3OH	71	22
c		5	CH_3OH	80	14
d		60	CH_3OH	45	7
e		2	CH_3OH	91	7
f		5	$\text{C}_2\text{H}_5\text{OH}$	95	2
g		5	$(\text{CH}_3)_3\text{COH}$	99	trace

i) 2 ml of alcohol was added.

ii) All compounds exhibited ir and nmr spectrum data in accordance with assigned structures.

iii) Paraldehyde was used.

It is well known that dihydromethoxypyrones[7], such as dihydrokawain[7c] and kawain[7d], exist in many natural sources. According to the present methods, namely, a) formation of hydroxyketoesters[3], b) lactonization, and c) methylation, 7c and 7d were easily prepared from β -phenylpropionaldehyde[2c] and cinnamaldehyde[2d] in overall 80% and 32% yields, respectively.

Further synthesis of the metabolite which has 5,6-dihydro-4-methoxy-2-pyrone skeleton is now in progress.

REFERENCES AND NOTES

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- 2) Recently, δ -hydroxy- β -ketoesters[3] were prepared by the reaction of 1,3-dianion generated from acetoacetic ester under strongly basic conditions with carbonyl compounds. S. N. Huckin and L. Weiler, Tetrahedron Lett., 4835 (1971); idem., Can. J. Chem., 52, 2157 (1974). It is the great contrast to our reaction under acidic conditions.
- 3) A. B. Boese, Jr., Ind. Eng. Chem., 32, 16 (1940).
- 4) Dihydromethoxypyrones[7] have hitherto been synthesized according to the following three procedures; namely, by the conjugate addition of methanol to 5-hydroxy-2-propionic esters⁵⁾ or by Reformatsky reaction from 4-bromo-3-methoxycrotonic esters⁶⁾ or by lactonization of δ -hydroxy- β -ketoesters[3] prepared by Weiler's dianion process.⁷⁾
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- 6) M. W. Klohs, F. Keller, and R. E. Williams, J. Org. Chem., 24, 1829 (1959).
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