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A CONVENIENT METHOD FOR THE SYNTHESIS OF 7-OXO-(E)-3-ALKENOIC ACIDS BY THE REACTION OF β-VINYL-β-PROPIOLACTONE WITH METALLATED N,N-DIMETHYLHYDRAZONES

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β-Vinyl-β-propiolactone reacts regio- and stereoselectively with an enolate equivalent such as cuprate derivatives of *N*,*N*-dimethylhydrazones and their bromomagnesium derivatives in the presence of a copper(I) catalyst to afford 7-oxo-(E)-3-alkenoic acids in high yields.

Carbon-carbon σ-bond formation, one of the most fundamental operation in organic chemistry, is often accomplished by a nucleophilic reaction of enol derivatives with organic substrates.[1)] In general, hard bases of charge-delocalized enolates such as lithium enolates undergo 1,2-addition to α,β-enones, although soft bases of charge-localized enolate such as sodium diethyl malonate undergo conjugate addition to their β carbon. On the other hand, by a recent report on the reaction of β-vinyl-β-propiolactone, the regioselectivity of various nucleophiles was found to depend on the hard and soft acid and base principle. Namely, the softness of the reaction sites of the lactone increases in the order of the acyl carbon, the β-carbon and the terminal vinyl carbon.[2)] For example, a soft base of diorganocuprate attacks predominantly at the terminal vinyl carbon of β-vinyl-β-propiolactone to give (E)-3-alkenoic acids in high yields.[3)] This reaction corresponds to 1,6-addition to α,β,γ,δ-dienoic acids, and is the five carbon homologation with two functional groups of a double bond predominant in the E form and a terminal carboxyl group. The utility of this reaction was demonstrated in the simple synthesis of royal jelly acids and queen substance.[4)] If the reaction of enolate anion with β-vinyl-β-propiolactone occurs similarly at the soft reaction site of the terminal vinyl carbon, it affords 7-oxo-3-alkenoic acids, which have three functional groups, such as a carbonyl function, a carbon-carbon double bond and a carboxylic function suitable for organic syntheses. We wish to describe here the reaction of β-vinyl-β-propiolactone with enolate equivalents of *N*,*N*-dimethylhydrazones providing one-step synthesis of 7-oxo-(E)-3-alkenoic acids.

The reaction of β-vinyl-β-propiolactone with a hard base of lithium enolate is expected to take place at the acyl carbon site of the lactone. In fact, when β-vinyl-β-propiolactone was treated with acetone lithium enolate, neither two kind of carboxylic acids formed by both S_N2 reaction at the β-carbon and S_N2' reaction at the terminal vinyl carbon, such as 7-oxo-3-octenoic acid and 5-oxo-3-vinylhexanoic acid, respectively, could be obtained. On the other hand, when acetone copper enolate, prepared from the lithium enolate and copper(I) iodide, was used, the reaction of β-vinyl-β-propiolactone gave the desired acids in a low yield of 21%.

Even the use of three equivalents of acetophenone copper enolate gave 7-phenyl-7-oxo-3-heptenoic acid along with 5-phenyl-5-oxo-3-vinylpentanoic acid in a maximal yield of 53% with the ratio of 88:12. Thus, softer bases of copper enolates than lithium enolates were found to react expectedly at the terminal vinyl carbon of β-vinyl-β-propiolactone to give 7-oxo-3-alkenoic acids mainly, although the yields were not satisfactory.

α-Lithiated acetone *N*,*N*-dimethylhydrazone is known to be more stable than acetone lithium enolate, and the cuprate derivative of acetone *N*,*N*-dimethylhydrazone undergoes clean 1,4-addition to α,β-unsaturated esters.5) Thus the reaction of β-vinyl-β-propiolactone with cuprate derivatives of *N*,*N*-dimethylhydrazones was performed. When β-vinyl-β-propiolactone was treated with cuprate derivative of acetone *N*,*N*-dimethylhydrazone, prepared from the corresponding lithiated hydrazone and copper(I) iodide, in THF-Me_2S at -78 °C for 1.5 h, followed by quenching with 3M HCl aqueous solution, the simultaneous hydrolysis of the hydrazone occurred, and 7-oxo-3-octenoic acid (1) were obtained along with 5-oxo-3-vinylhexanoic acid (2) in 72% yield with the ratio of 87:13. The reaction at -100 °C for 2 h increased both the yield and the regioselectivity. Furthermore, the metal cation exchange from lithium into halomagnesium increased the yield up to 91%, and the ratio of the acids was up to 92:8. These results are summarized in Table I. The following procedure is representative. Lithiated acetone *N*,*N*-dimethylhydrazone in THF was exchanged into a bromomagnesium derivative by the addition of magnesium dibromide at -30 °C. Subsequent reaction with a half equivalent of copper(I) iodide in THF-Me_2S at -30 °C for 1 h and then with 0.45 equivalent of β-vinyl-β-propiolactone at -100 °C for 2 h gave the desired acids. Acetaldehyde *N*,*N*-dimethylhydrazone was also converted into 7-oxo-3-heptenoic acid along with 5-oxo-3-vinylpentanoic acid in a yield of 51% with the ratio of 93:7. The stereochemistry of newly formed double bond in these products was found to be E isomer predominant more than 93% by a capillary glpc.

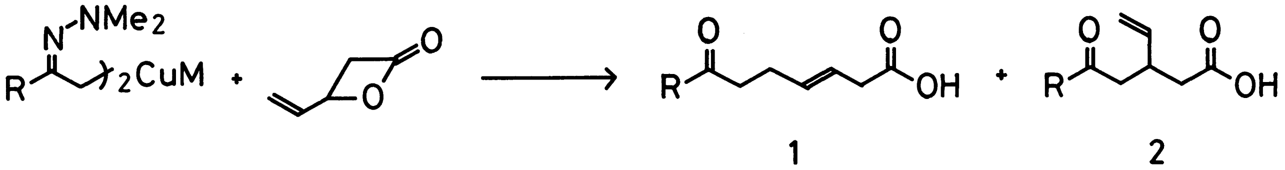
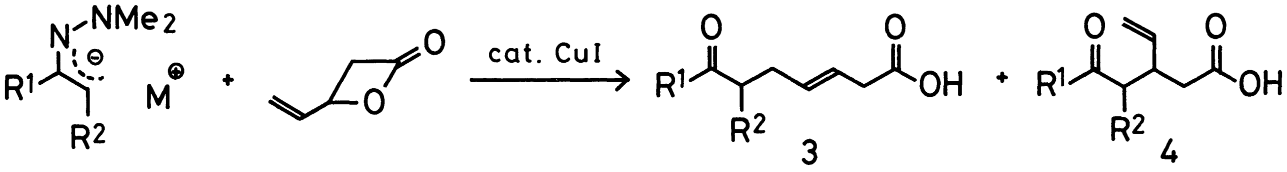


Table I. Reaction of β-Vinyl-β-propiolactone with Cuprates of *N*,*N*-Dimethylhydrazones[a]

R	M	Temp (°C)	Time (h)	Yield(%) 1 + 2	Product Ratio[b] 1 : 2	E-1 : Z-1
Me	Li	-78	1.5	72	87 : 13	96 : 4
Me	Li	-100	2	88	89 : 11	96 : 4
Me	MgBr	-100	2	91	92 : 8	98 : 2
H	MgBr	-100	3	51	93 : 7	93 : 7

[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] The ratios were determined by a capillary glpc analysis (FFAP, 50 m).

In analogy with the reaction of β-propiolactone with organocopper reagents,[6)] the copper catalyzed reaction of the metallated *N*,*N*-dimethylhydrazones with β-vinyl-β-propiolactone was also successfully carried out. When the lactone reacted with lithiated acetone *N*,*N*-dimethylhydrazone in the presence of copper(I) iodide (10 mol%) in THF-Me_2S at -100 °C, 7-oxo-3-octenoic acid was obtained along with 5-oxo-3-vinylhexanoic acid in 79% yield. In contrast, the use of bromomagnesium derivative in place of the lithium derivative increased the yield of the corresponding acids up to 83%. In addition, glpc analysis showed the ratio of the both acids as 98:2. The results of the copper catalyzed reaction using various *N*,*N*-dimethylhydrazones[7)] are summarized in Table II. Methyl ethyl ketone *N*,*N*-dimethylhydrazone reacted exclusively at the methyl site of methyl ethyl ketone to give 7-oxo-3-nonenoic acid along with 5-oxo-3-vinylheptanoic acid in a high yield. The reaction of the lactone with cyclohexanone *N*,*N*-dimethylhydrazone gave exclusively the S_N2' type of product by an attack of the organometal at the terminal vinyl carbon of the lactone. The stereochemistry of the double bond formed at the 3 position of 7-oxo-3-alkenoic acids was also found to be E isomer predominant more than 91%. In the case of acetaldehyde *N*,*N*-dimethylhydrazone, the reaction using cuprate derivative gave a similar result as the copper catalyzed reaction.



The following procedure for the synthesis of 7-oxo-3-octenoic acid is representative for the copper catalyzed reaction. Copper(I) iodide (30 mg, 0.15 mmol) was dissolved in THF (3 ml) and Me_2S (0.1 ml) under argon. After cooling to -100 °C, β-vinyl-β-propiolactone (0.10 g, 1 mmol) in THF (2 ml) and then bromomagnesium acetone *N*,*N*-dimethylhydrazone (0.25M in THF, 1.5 mmol) were slowly added. The mixture was stirred at -100 °C for 2 h and quenched by adding 3M aqueous

Table II. Reaction of β-Vinyl-β-propiolactone with Various Metallated *N*,*N*-Dimethylhydrazones in the Presence of Copper(I) Iodide[a]

R	R	M	Temp (°C)	Time (h)	Yield(%) 3 + 4	Product Ratio[b]	
						3 : 4	E-3 : Z-3
Me	H	Li	-100	2	79	85 : 15	96 : 4
Me	H	MgBr	-100	2	83	98 : 2	96 : 4
Et	H	MgBr	-100	2	76	99 : 1	96 : 4
Ph	H	MgBr	-100	3	81	99 : 1	96 : 4
$-(CH_2)_4-$		MgBr	-100	3	84	100 : 0	97 : 3
H	H	MgBr	-100 ∿ -30	2.5	47	96 : 4	91 : 9

[a] All reactions were carried out on 1 mmol scales with the procedure as described in the text. All products were identified by IR and NMR spectra. [b] The ratios were determined by a capillary glpc analysis (FFAP, 50 m).

solution. 7-Oxo-3-octenoic acid was extracted with saturated sodium bicarbonate solution from the organic layer. The alkaline solution was acidified and extracted with ether and concentration gave the desired acid containing 2% of 5-oxo-3-vinylhexanoic acid in a yield of 83%.

In the reaction of β-vinyl-β-propiolactone with various nucleophiles, the mode of the ring opening depended on the nature of the nucleophiles.$^{2)}$ In the case of the reaction with enolate equivalents, the ratio of the reaction mode was also found to depend on the metal cation of the enolate equivalents. The ratio of the S_N2' type reaction products were increased when metal cation of metallated *N*,*N*-dimethylhydrazones was exchanged to a soft cation of magnesium from a hard cation of lithium. Thus, the reaction of β-vinyl-β-propiolactone with halomagnesium derivatives of *N*,*N*-dimethylhydrazones in the presence of a copper(I) catalyst or with halomagnesium cuprate derivatives of *N*,*N*-dimethylhydrazones afforded 7-oxo-(E)-3-alkenoic acids in high yields. Although the preparation of methyl 7-oxo-3-octenoate$^{9)}$ by the palladium catalyzed oxidation of the terminal double bond of methyl 3,7-octadienoate, and ethyl 7-oxo-3-heptenoate$^{10)}$ by photochemical reaction of ethyl 2-oxo-1-cyclohexanecarboxylate were reported, the following advantages render the present reaction attractive: 1) the easily availability of the *N*,*N*-dimethylhydrazones and β-vinyl-β-propiolactone, 2) one-step synthesis and the simplicity of the experimental procedures, 3) high yields of 7-oxo-3-alkenoic acids, and 4) highly stereoselective double bond formation at the 3 position of the acids.

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