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# A CONVENIENT METHOD FOR THE SYNTHESIS OF (E)-3-ALKENOIC ACIDS BY A REGIO- AND STEREOSELECTIVE REACTION OF β-VINYL-β-PROPIOLACTONE WITH ORGANOCOPPER REAGENTS

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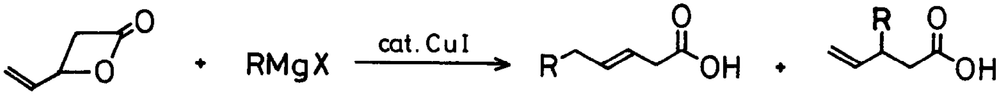
Summary: *β-Vinyl-β-propiolactone reacts regio- and stereoselectively with Grignard reagents in the presence of copper(I) catalyst or with diorganocuprates to afford (E)-3-alkenoic acids in high yields.*

Nucleophilic substitution of allylic substrates with organometallic reagents provides a facile method for the synthesis of olefinic compounds. Regioselectivity (either $S_N2$ or $S_N2'$ reaction) and stereoselectivity (stereochemistry of newly formed double bond) of the reaction in allylic systems are important problems for the controlled synthesis of olefinic compounds.[1] Recently, we have reported that highly regioselective reaction of β-propiolactones with diorganocuprates[2] or with Grignard reagents in the presence of copper(I) catalyst[3] affords β-substituted propionic acids in excellent yields. On the other hand, β-vinyl-β-propiolactone,[4] which corresponds to an allylic ester,[5] is considered to have three reaction points towards nucleophiles, i.e. the terminal vinyl carbon ($S_N2'$ type), the β-carbon ($S_N2$ type)[6] and the carbonyl carbon. If β-vinyl-β-propiolactone could undergo selectively $S_N2'$ reaction with organometallic reagents, it will provide a new five-carbon homologation leading to the corresponding 3-alkenoic acids. We now wish to report a new general method for the synthesis of (E)-3-alkenoic acids by the regio- and stereoselective reaction of β-vinyl-β-propiolactone with organocopper reagents.

When β-vinyl-β-propiolactone (1 equiv) was treated with butylmagnesium bromide (1.1 ~ 1.2 equiv) in the presence of copper(I) iodide (2 mol%) in THF at -30 °C, two kinds of carboxylic acids formed by both the $S_N2'$ and $S_N2$ reactions, 3-nonenoic acid (**1**; R = Bu) and 3-butyl-4-pentenoic acid (**2**; R = Bu), were obtained in 91% yield without accompanying any product by the addition to the carbonyl carbon. Glpc analysis of the acids showed the ratio of 3-nonenoic acid to 3-butyl-4-pentenoic acid as 98 : 2, indicating that the reaction proceeds regioselectively through $S_N2'$ pathway. When homogeneous reaction using butylmagnesium bromide was carried out by adding dimethyl sulfide as a co-solvent of THF to dissolve the copper catalyst, the yield of the corresponding acids was increased to 96% with the same ratio of 1 and 2. Ether, instead of THF was employed as a solvent to result in decreasing both the yield (68%) and regioselectivity (1 : 2 = 80 : 20). It should be noted that without copper catalyst, the reaction of the lactone with butylmagnesium bromide in THF at -30 °C for 15 min gave less than 11% of 3-nonenoic acid along with many by-products.



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The copper-catalyzed reaction of butylmagnesium bromide with β-vinyl-β-propiolactone in THF-Me$_2$S was performed at various reaction temperatures, and the results were summarized in Table I. High regioselectivity by the $S_N2'$ reaction was exhibited at lower temperature. When the reaction was carried out at -100 °C for 15 min, 3-nonenoic acid was obtained in a high yield of 94% along with only trace amounts of 3-butyl-4-pentenoic acid. Stereochemistry of the double bond of 3-nonenoic acid was also affected by the reaction temperature, and the E isomer was formed predominatly at lower temperature. The reaction at -100 °C gave 3-nonenoic acid in a ratio[7] of the E isomer to Z isomer of 90 : 10.

The reaction of several representative Grignard reagents in the presence of copper catalyst with β-vinyl-β-propiolactone was examined as shown in Table II. Grignard reagents attacked regioselectively almost only at the terminal vinyl-carbon of the lactone to afford (E)-3-alkenoic acids in high yields with high stereochemical purity (ca. 90%), whether the substituent is primary, secondary,

Table I. Effect of Reaction Temperature on the Regioselectivity and Stereoselectivity in the Copper-Catalyzed Reaction of BuMgBr with β-Vinyl-β-propiolactone[a]

| Temp(°C) | Yield(%) of 1 + 2 | Product Ratio[b] | |
|---|---|---|---|
| | | 1 : 2 | (E)-1 : (Z)-1 |
| 0 | 94 | 87 : 13 | 74 : 26 |
| -30 | 96 | 98 : 2 | 84 : 16 |
| -78 | 96 | 99 : 1 | 87 : 13 |
| -100 | 94 | >99 : <1 | 90 : 10 |

[a] All reactions were performed on 2 mmol scales in THF-Me$_2$S (20 : 1) for 15 min. The molar ratio of RMgX and the lactone is 1.2 : 1.0. [b] Determined by glpc analysis.

or tertiary alkyl group. The reaction of phenylmagnesium bromide proceeded with slightly decrease both in regio- and stereoselectivity. However, vinyl- and allylmagnesium bromides gave the corresponding acids in low yields.

Diorganocuprates were also found to react regio- and stereoselectively with β-vinyl-β-propiolactone. When the lactone was treated with dibutylcuprate, prepared from one equivalent of copper(I) iodide and two equivalent of butylmagnesium bromide, in THF-$Me_2S$ (10 : 1) at -78 °C for 1 h, 3-nonenoic acid was obtained in a yield of 92% (E : Z = 89 : 11) along with a small amount of 3-butyl-4-pentenoic acid (2%). In contrast to the poor result of the copper-catalyzed reaction of allylmagnesium bromide, the reaction using diallylcuprate proceeded with higher regio- and stereoselectivity to give (E)-3,7-octadienoic acid in 86% yield (E : Z = 89 : 11). However, in the case of divinylcuprate, the result was not improved.

The following procedure for the synthesis of (E)-3-nonenoic acid is repre-

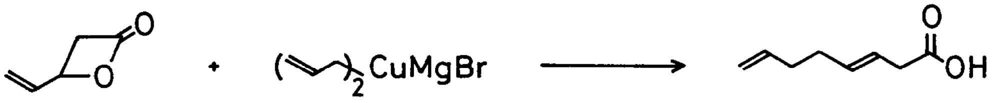
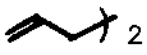


Table II. Reaction of Various Grignard Reagents with β-Vinyl-β-propiolactone in the Presence of Copper(I) Iodide [a]

| RMgX | Temp (°C) | Time (min) | Yield(%) of 1 + 2 | Product Ratio 1 : 2 | (E)-1 : (Z)-1 |
|---|---|---|---|---|---|
| MeMgBr | -100 | 15 | 70 | 97 : 3 | 92 : 8 |
| EtMgBr | -100 | 15 | 91 | 99 : 1 | 89 : 11 |
| BuMgBr | -100 | 15 | 94 | >99 : <1 | 90 : 10 |
| s-BuMgCl | -100 | 15 | 96 | >99 : <1 | 88 : 12 |
| i-BuMgBr | -100 | 15 | 90 | >99 : <1 | 88 : 12 |
| t-BuMgCl | -78 | 50 | 84 | 100 : 0 | 86 : 14 |
| PhMgBr | -100 | 15 | 91 | 91 : 9 | 83 : 17 |
| MgBr | -78 | 30 | 61 | 92 : 8 | 78 : 22 |
|  MgBr | -50 | 120 | 25 | 87 : 13 | 77 : 23 |
| $Bu_2CuMgBr$ [b] | -78 | 60 | 92 | 99 : 1 | 89 : 11 |
| ($_2$CuMgBr [b] | -50 | 60 | 64 | 87 : 13 | 82 : 18 |
| ($_2$CuMgBr [b] | -50 | 60 | 88 | 98 : 2 | 89 : 11 |

[a] All reactions were carried out on 2 mmol scales with the same procedure as described in the text. All products were identified by IR and NMR spectra. Product ratio was determined by glpc analysis. [b] In these cases, diorganocuprates were used.

sentative for the copper-catalyzed reaction. Copper(I) iodide (9 mmg, 0.04 mmol) was dissolved in 0.5 ml of $Me_2S$ and 8 ml of THF under argon. After cooling to -100 °C, β-vinyl-β-propiolactone (0.196 g, 2 mmol) in 2 ml of THF and then butylmagnesium bromide (1.0 M in THF, 2.4 mmol) were slowly added. The mixture was stirred at -100 °C for 15 min and quenched by adding 3N HCl solution. (E)-3-Nonenoic acid was extracted with 3N NaOH solution from the organic layer. The alkaline solution was acidified and extraction with ether and concentration gave the desired acid (94%).

Although 1,6-addition of organocopper reagents to α,β,γ,δ-dienoates or dienoic acids has been known to give (E)-3-alkenoic acid derivatives,[8] the following advantages render the present reaction attractive: (1) the readily availability of the lactone, (2) the simplicity of the experimental procedures, and (3) an equimolar amount of Grignard reagents to the lactone was sufficient for the completion of the reaction.

## References and Notes

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