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COPPER-CATALYZED REACTION OF GRIGNARD REAGENTS WITH β-PROPIOLACTONES: A CONVENIENT METHOD FOR THE SYNTHESIS OF β-SUBSTITUTED PROPIONIC ACIDS

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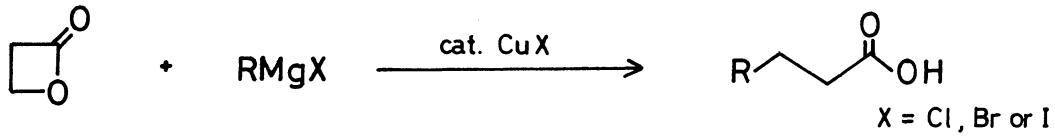
Grignard reagents react with β-propiolactones in the presence of a copper(I) catalyst to give β-substituted propionic acids in high yields.

Copper-catalyzed reaction of Grignard reagents is an extensively useful method for a new carbon-carbon bond formation; representatives are the substitution reactions[1] with organic halides, tosylates, and allylic acetates, and the conjugate addition to α,β-unsaturated carbonyl compounds.[2,3] Recently, Huynh et al. have reported that ring-opening of cyclic ethers such as oxiranes and oxetanes by Grignard reagents is also accelerated by a copper(I) catalyst.[4] A previous study by Gresham et al. has shown that Grignard reagents react with β-propiolactone to afford a mixture of β-halopropionic acids, vinyl ketones, β-substituted propionic acids, etc.[5] If the β-substituted acids could be selectively formed by this reaction, it will provide a useful method for three carbon homologation terminating with a carboxyl function. We wish to report here the regiospecific reaction of Grignard reagents with β-propiolactones in the presence of a copper(I) catalyst which affords β-substituted propionic acids in high yields.



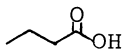
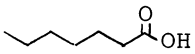
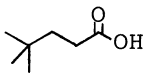
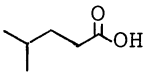
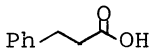
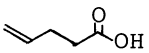
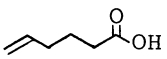
When β-propiolactone (1 equiv) was treated with butylmagnesium bromide (1.2 equiv) and copper(I) chloride (0.02 equiv) in THF at 0 °C for 15 min, heptanoic acid was obtained in 90% yield. Copper(I) bromide and iodide showed a similar effect as the catalyst. Since copper(I) salts were insoluble in THF, homogeneous reaction using butylmagnesium bromide and copper(I) iodide was carried out by

adding dimethyl sulfide as a co-solvent of THF, but the yield of the acid was not affected. Ether, instead of THF, was employed as a solvent to result in a decrease in the yield (50%).

The reaction of several representative Grignard reagents with β-propiolactone was studied as shown in Table I. Grignard reagents attacked regiospecifically the methylene carbon of β-propiolactone to afford β-substituted propionic acids in good yields, whether the substituent is primary, secondary, or tertiary alkyl group, or phenyl group. Vinylmagnesium bromide gave the corresponding acid in a moderate yield. However, allylmagnesium bromide gave only a trace amount of 5-hexenoic acid.[6)]

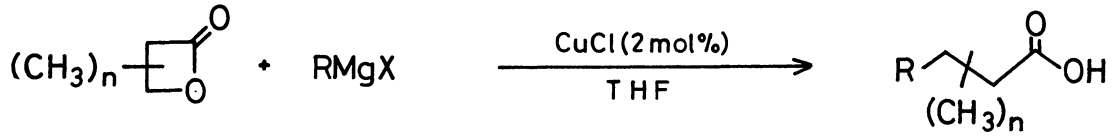
In order to find the scope and limitations of the ring-opening reaction, the reaction of methyl-substituted β-propiolactones with the Grignard reagents in the presence of a copper(I) catalyst was examined. The result is shown in Table II. Butylmagnesium bromide reacted with α-methyl, β-methyl- and α,α-dimethyl-β-propiolactones to give the β-substituted propionic acids in yields of over 80%. In the case of the other Grignard reagents, however, the introduction of a substituent on the lactone ring affected largely the yields of the corresponding acids. In the

Table I. Reaction of β-Propiolactone with Grignard Reagents in the Presence of CuCl[a]

RMgX	Product	Yield glc	Yield isolated
MeMgBr		89	87
BuMgBr		90	90
t-BuMgCl		89	85
i-PrMgBr		78	74
PhMgBr		78	77
CH_2=CHMgBr		67	59
CH_2=$CHCH_2$MgBr		trace	-

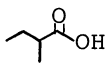
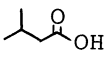
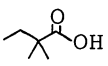
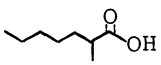
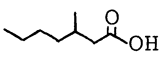
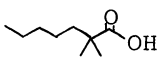
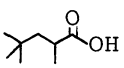
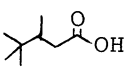
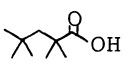
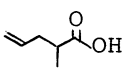
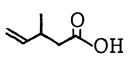
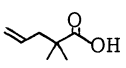
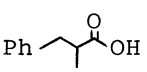
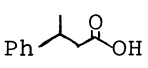
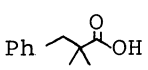
[a] All reactions were performed on 2 mmol scales at 0 °C for 15 min. The molar ratio of RMgX and β-propiolactone is 1.2:1.0. The yields were based on β-propiolactone.

case of the reaction of t-butylmagnesium chloride, α-methyl- and β-methyl-β-propiolactones showed similar reactivity to that of unsubstituted one. On the other hand, α,α-dimethyl one gave the corresponding acid in much lower yield due to simultaneous formation of pivalic acid, a reductive ring-opening product. In the case of the reaction of methylmagnesium bromide, α-methyl- and α,α-dimethyl-β-propiolactones afforded the desired acids in more than 80% yield, whereas β-methyl one gave isovaleric acid in 52% yields. The reaction of Grignard reagents with sp^2 carbon atom such as phenyl and vinyl groups with β-methyl- and α,α-dimethyl-β-propiolactones gave only small amounts of the desired acids.



The following procedure for the synthesis of heptanoic acid is representative. Butylmagnesium bromide (1.0M in ether, 2.4 mmol) was slowly added to a suspension of CuCl (4 mg, 0.04 mmol) in 6 ml of THF at 0 °C under argon. Then, β-propiolactone (0.144g, 2 mmol) in 2 ml of THF was added dropwise. The mixture was stirred at 0 °C for 15 min and quenched by adding 3N HCl solution. Heptanoic acid was extracted

Table II. Products and Yields (%) of the Copper-Catalyzed Reaction of Grignard Reagents with Methyl-Substituted β-Propiolactones[a]

Reactant			
MeMgBr	 (83)	 (52)	 (80)
BuMgBr	 (89)	 (81)	 (79)
t-BuMgCl	 (89)	 (84)	 (24)[b]
CH_2=CHMgBr	 (60)[b,c]	 (trace)	 (trace)
PhMgBr	 (52)	 (13)	 (8)[b]

[a] All reactions catalyzed by CuCl were performed on 2 mmol scales at 0 °C for 15 min, and the yields were isolated ones unless otherwise noted. [b] Yields were determined by NMR. [c] Reaction was carried out at -30 °C for 2 h .

with 3N NaOH solution from the organic layer. The alkaline solution was acidified, and extraction with ether and concentration gave pure heptanoic acid (90%).

Recently, we reported the regiospecific ring-opening of β-propiolactones by diorganocuprates.[7] Although the reaction of divinyl- and diallylcuprates afforded the corresponding acids in higher yields than those obtained by the reaction of Grignard reagents, the copper-catalyzed reaction of Grignard reagents has some advantages as follows: (1) an equimolecular amount of the Grignard reagent to β-propiolactone was sufficient for the completion of the reaction, and (2) a simplicity of the operative conditions such as, short reaction time and moderate reaction temperature. Thus, the ring-opening of β-propiolactones with Grignard reagents provides a convenient procedure for the synthesis of β-substituted propionic acids, which is alternative to the conjugate addition of organometallic compounds to α,β-unsaturated acids or esters.[8]

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References and Notes

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4) C. Huynh, F. Derguini-Boumechal, and G. Linstrumelle, *Tetrahedron Lett.*, 1503 (1979).

5) (a) T. L. Gresham, J. E. Jansen, F. W. Shaver, and R. A. Bandert, *J. Am. Chem. Soc.*, 71, 2807 (1949); (b) C. G. Stuckwisch and J. V. Bailey, *J. Org. Chem.*, 28, 2362 (1963).

6) Allylmagnesium bromide attacked exclusively the carbonyl carbon of β-propiolactone to result in a formation of 3-allyl-5-hexene-1,3-diol as a main product. On the contrary, Stuckwisch et al. reported that the reaction of β-propiolactone with allylmagnesium bromide without a copper catalyst in ether gave 5-hexenoic acid in 54% yield.[5b]

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