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ONE-STEP SYNTHESIS OF HOMOTERPENOIC CARBOXYLIC ACIDS FROM β-ISOPROPENYL-β-PROPIOLACTONE AND ORGANOCOPPER REAGENTS

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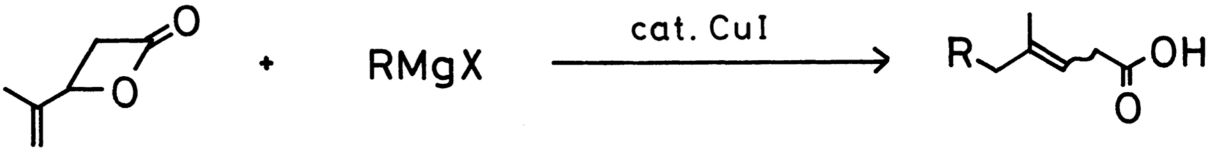
Regioselective reaction of Grignard reagents in the presence of a copper(I) catalyst or of organocuprates with the terminal vinyl carbon of β-isopropenyl-β-propiolactone through the S_N2' pathway affords 4-methyl-3-alkenoic acids in which the (E)-isomers predominate in good yields. Synthetic utility of this reaction is demonstrated in one-step synthesis of homoterpenoic carboxylic acids.

Homoterpenoic carboxylic acids or their derivatives have been employed as useful precursors for the synthesis of several natural products. For example, homogeranic acid was used as an intermediate for the syntheses of squalene,[1] dihydroactinidiolide,[2] and moenocinol.[3] Homofarnesylic acid and its derivatives were used for the syntheses of α-bisabololfarnesylcarboxylate[4] which shows anti-ulcer and antiinflammatory activities, 3,7,11,15-tetramethylhexadeca-6,10-trans, trans-14-trien-1-ol[5] which is an odoriferous compound, and 19-nor-testosteron homofarnesate[6] used as anabolic pharmaceuticals.

The conventional process for the preparation of homoterpenoic carboxylic acids consists of multi steps, e.g. $RCH_2OH \rightarrow RCH_2Hal \rightarrow RCH_2CN \rightarrow RCH_2CO_2H$.[2] Two-step conversion of geranyl bromide to homogeranyl iodide *via* sulfide using phenylthiomethyl copper has been reported by Corey.[7] The preparation of homogeranyl bromide and iodide by the reaction of methyl cyclopropyl ketone and homoprenyl Grignard reagent has been developed by Julia[8] and its useful modification to one step procedure has been reported by Biernacki.[9] But the synthesis of homoterpenoic carboxylic acids from the homoterpenoic halides needs the oxidation process to a carboxyl group and one-step synthesis of homoterpenoic carboxylic acids has not yet been reported to our knowledge.

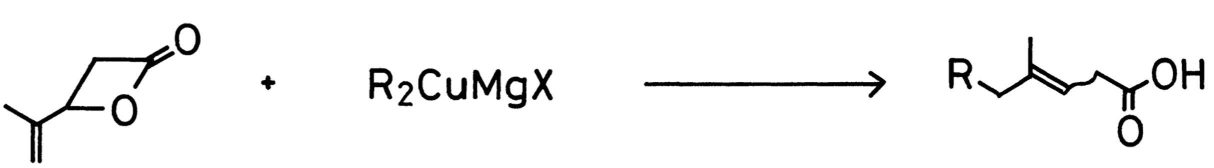
β-Isopropenyl-β-propiolactone, easily prepared by 1,2-cycloaddition of ketene and methacroleine,[10] corresponds to an allylic ester, and just fits as a building brock of C_6 unit for the synthesis of the homoterpenoic carboxylic acids. If the organocopper reagents attack regioselectively the terminal vinyl carbon of the lactone through the S_N2' pathway, 5-substituted 4-methyl-3-pentenoic acids, which possess the homoterpenoic skeleton, may be obtained. Moreover, terpenoic organocopper reagents may give homoterpenoic carboxylic acids such as homogeranic acid and homofarnesylic acid by the reaction with β-isopropenyl-β-propiolactone in one pot procedure. We describe here the reaction of β-isopropenyl-β-propiolactone with organocopper reagents and one-step synthesis of homoterpenoic acids utilizing this reaction.

Butylmagnesium bromide (1.1 equiv) was added dropwise to a -78 °C solution of β-isopropenyl-β-propiolactone (1 equiv) and copper(I) iodide (2 mol%) in THF and Me$_2$S (10:1). After the solution was stirred for 1 h at -78 °C, 3N hydrochloric acid was added. The mixture was extracted with ether and the combined ether layers were washed with 3N aqueous sodium hydroxide. The aqueous solution was acidified, extracted with ether and the combined ether layers were washed with brine. Drying with MgSO$_4$ and evaporation of solvents at reduced pressure afforded a crude acid. The crude acid was distilled at reduced pressure by bulb-to-bulb to give a pure 4-methyl-3-nonenoic acid in a high yield of 92% without any accompanying product through S$_N$2 pathway. Glpc analysis of this acid showed the ratio of the E isomer to Z isomer of 73:27. Ether instead of THF was employed as a solvent to result in increasing the yield (96%), but in decreasing the stereoselectivity (49:51).



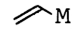
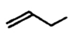
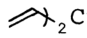
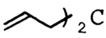
The copper-catalyzed reaction of various Grignard reagents with β-isopropenyl-β-propiolactone was shown in Table I. Grignard reagents with primary, secondary, and tertiary alkyl groups, and phenyl group furnished the corresponding 4-methyl-3-alkenoic acids in good yields, respectively. When Grignard reagents with vinyl and allyl groups as the substituents were used, the yields of the corresponding acids were decreased.

Diallylcuprate gives a better yield rather than allylmagnesium bromide in the presence of a copper(I) salt in the reaction with β-propiolactone.[11] In the case of β-isopropenyl-β-propiolactone, bromomagnesium diallylcuprate, prepared from allylmagnesium bromide (2.2 equiv) and copper(I) iodide (1.1 equiv), reacted also easily with the lactone in THF-Me$_2$S (10:1) at -30 °C for 1 h and then at 0 °C for 1.5 h and the yield of 4-methyl-3,7-octadienoic acid was improved to 57%. On the other hand, bromomagnesium divinylcuprate, prepared from vinylmagnesium bromide (2.2 equiv) and copper(I) iodide (1.1 equiv), afforded 4-methyl-3,6-heptadienoic acid in almost unaltered yield with the use of vinylmagnesium bromide.



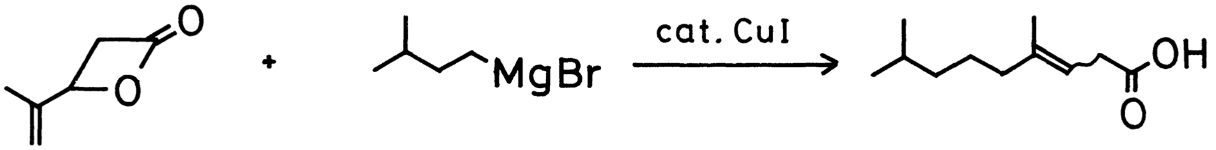
For the stereochemistry of the products, the ratio of the E isomer to Z isomer was ca. 75:25 except for methylmagnesium bromide, allylmagnesium bromide and bromomagnesium divinylcuprate of ca. 68:32. Compared with the reaction of β-vinyl-β-propiolactone previously reported,[12] the reaction of β-isopropenyl-β-propiolactone with these organometallics was found to give exclusively the regioselective products by S$_N$2' reaction without any products through S$_N$2 pathway, but the stereoselectivity somewhat decreased.

Table I. Reaction of the Representative Grignard Reagents with β-Isopropenyl-β-Propiolactone in the Presence of Copper(I) Iodide[a]

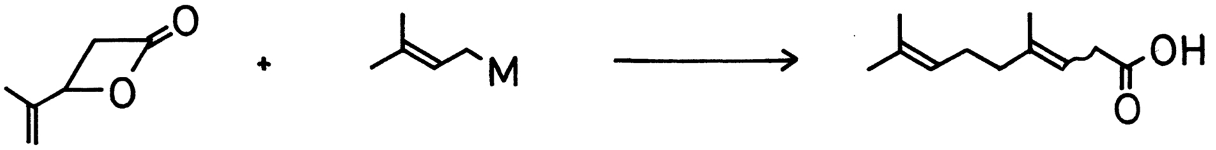
RMgX	Yield(%)	Product Ratio[b] E : Z	RMgX	Yield(%)	Product Ratio[b] E : Z
MeMgBr	80	66 : 34	PhMgBr	84	72 : 28
EtMgBr	88	73 : 27	MgBr	>48	74 : 26
BuMgBr	92	73 : 27	MgBr[c]	20	68 : 32
s-BuMgCl	91	76 : 24	$_2$CuMgBr[d]	49	69 : 31
t-BuMgCl	88	72 : 28	$_2$CuMgBr[e]	57	76 : 24

[a] All reactions were performed on 2 mmol scales at -78 °C (1 h) unless otherwise noted. The molar ratio of RMgX and the lactone is 1.1:1.0. All products were identified by IR and NMR spectra. Isolated by bulb-to-bulb distillation. [b] Determined by glpc analysis. [c] The reaction was carried out at -30 °C for 1 h and then at 0 °C for 2 h. [d] The reaction with divinylcuprate was carried out at -30 °C for 1 h and then at 0 °C for 1.5 h. [e] The reaction with diallylcuprate was carried out at -30 °C for 1 h and then at 0 °C for 1.5 h.

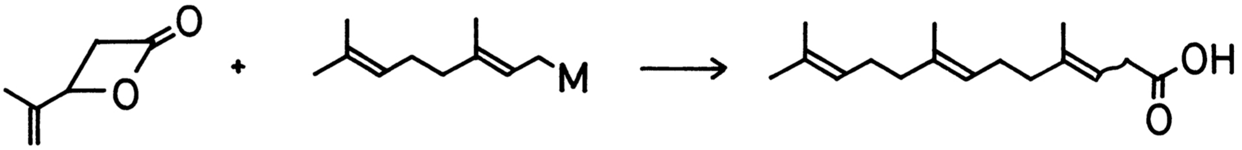
Since the regioselective reaction of representative Grignard reagents with the lactone gave the 4-methyl-3-alkenoic acids in which the E isomers predominate in good yields, we next examined the one-step synthesis of homoterpenoic carboxylic acids. Firstly, the synthesis of 4,8-dimethyl-3-nonenoic acid employed as a useful precursor for the synthesis of phythol was demonstrated. When β-isopropenyl-β-propiolactone was treated with isoamylmagnesium bromide in the presence of copper(I) iodide (2 mol%) in THF-Me_2S (20:1) at -78 °C for 1 h, 4,8-dimethyl-3-nonenoic acid[13] (E:Z = 71:29) was obtained in 85% yield.



Homogeranic acid[13] (E:Z = 72:28) was obtained in a moderate yield of 47% by the copper-catalyzed reaction of prenylmagnesium chloride with β-isopropenyl-β-propiolactone in THF-Me_2S (20:1) at -50 °C for 1 h and then -10 °C for 2 h. Since the reaction of diallylcuprate was superior to the copper-catalyzed reaction of allylmagnesium bromide, chloromagnesium diprenylcuprate was employed for the reaction of β-isopropenyl-β-propiolactone. Diprenylcuprate, prepared from prenylmagnesium chloride (2.2 equiv) and copper(I) iodide (1.1 equiv), easily reacted with the lactone in THF-Me_2S (10:1) at -50 °C for 1 h and then -10 °C for 2 h, and the yield of homogeranic acid[13] was expectedly increased to 89% (E:Z = 75:25).



Homofarnesylic acid[13] (E:Z = 78:22) was also obtained in 51% yield by the reaction of β-isopropenyl-β-propiolactone with geranylmagnesium chloride in the presence of copper(I) iodide in THF-Me_2S (20:1) at -50 °C for 1 h and then -30 °C for 1.5 h. By the use of chloromagnesium digeranylcuprate, prepared from geranylmagnesium chloride (2.2 equiv) and copper(I) iodide (1.1 equiv), the reaction with the lactone (1 equiv) in THF-Me_2S (10:1) at -50 °C for 1 h and then -30 °C for 1.5 h yielded homofarnesylic acid[13] (E:Z = 78:22) in 68% yield.



Thus, β-isopropenyl-β-propiolactone is found to be a useful synthon for the preparation of several natural products, since the carboxyl group of homoterpenoic carboxylic acids obtained by the regioselective reaction with organocopper reagents can be effectively used for chain lengthening reactions. The easy availability of the starting lactone and the simplicity of the experimental procedures make this method a synthetically useful one-step procedure for preparing homoterpenoic carboxylic acids.

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13. The structures of these acids were verified by compatible spectral data, and the ratio of E:Z was determined by capillary glpc analysis (F.F.A.P. 50m).

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