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ONE-STEP SYNTHESIS OF ω-HYDROXYCARBOXYLIC ACIDS BY THE REACTION OF ω-METALOXYLATED GRIGNARD REAGENTS WITH β-PROPIOLACTONES

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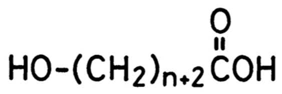
ω-Metaloxylated Grignard reagents reacted with β-propiolactones chemo- and regioselectively in the presence of Li_2CuCl_4 to afford ω-hydroxycarboxylic acids in high yields.

ω-Hydroxycarboxylic acids (1) are widely distributed throughout plants as the principal element of vegetable wax forming polyesters, and they are precursors of macrolides which have many physiological activities.[1)] Especially alicyclic lactones of $C_{13} \sim C_{15}$ ω-hydroxycarboxylic acids have proved to possess a musk or amber odor, and they are, therefore, important in the perfume industry. The syntheses of ω-hydroxycarboxylic acids (1) reported so far[2)] are generally troublesome; e.g. the controlled oxidation of either diols or hydroxy aldehydes, selective reduction of oxocarboxylic esters or dicarboxylic esters, hydrolysis of lactones synthesized by the Baeyer-Villiger oxidation of cyclic ketones,[3)] and so on. We wish to report here a convenient method for the synthesis of ω-hydroxycarboxylic acids (1) from easily abvailable ω-chloroalcohols (2) and β-propiolactones.

Recently the regioselective ring-opening reaction of β-propiolactones with the Grignard reagents in the presence of copper(I) catalyst has been reported to give β-substituted propionic acids in high yields.[4)] This reaction is a useful method for three carbon homologation terminating with a carboxyl function. Although the reaction of β-propiolactones with alkoxide is well known,[5)] we found that ω-metaloxylated Grignard reagents (3)[6)] reacted with β-propiolactone (4) in the presence of a copper catalyst to give various ω-hydroxycarboxylic acids (1). Namely, alkoxide part in metaloxylated Grignard reagents (3) does not react with β-propiolactone (4), whereas Grignard reagent part only reacts at β-carbon position of the lactone (4) chemo- and regioselectively.

Since ω-metaloxylated Grignard reagents (3) are easily derived from chloroalcohols (2), this procedure provides a short step synthesis of ω-hydroxycarboxylic acids (1) from β-propiolactone (4) and chloroalcohols (2) without protection of hydroxyl group. A kind of copper catalysts was examined in the reaction of the lactone (4) with metaloxylated Grignard reagent prepared from 12-chlorododecanol. The yields of 15-hydroxypentadecanoic acid were as follows; $CuI\text{-}Me_2S$ 60%, $CuI\text{-}(MeO)_3P$ 64%, $CuI\text{-}nBu_3P$ 80%, Li_2CuCl_4 86% (used 5 mol% catalyst). Li_2CuCl_4 was found to be the best catalyst. General procedure is as follows. To a solution of ω-chloroalcohol (2) in THF is added one equivalent of isopropylmagnesium chloride



$HO\text{-}(CH_2)_{n+2}\overset{O}{\overset{\|}{C}}OH$

1

$HO\text{-}(CH_2)_n\text{-}Cl$

2

$ClMgO\text{-}(CH_2)_nMgCl$

3

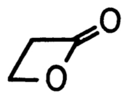


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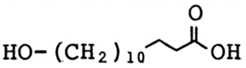
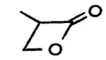
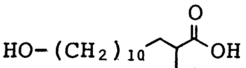
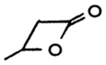
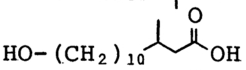
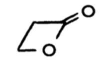
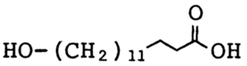
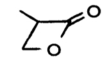
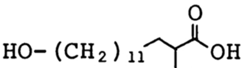
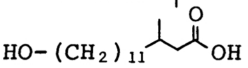
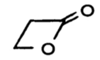
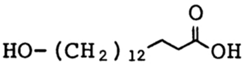
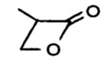
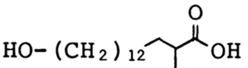
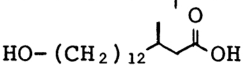
Table Yields of ω-Hydroxycarboxylic Acids[a]

Grignard Reagent	Lactone	Product	Mp(°C)	Yield(%)
ClMgO-$(CH_2)_{10}$-MgCl			76 ∿ 77 (78)[b]	90
ClMgO-$(CH_2)_{10}$-MgCl			55 ∿ 56 (55 ∿ 56.5)[c]	87
ClMgO-$(CH_2)_{10}$-MgCl			49 ∿ 50	73
ClMgO-$(CH_2)_{11}$-MgCl			90 ∿ 91 (91)[b]	84
ClMgO-$(CH_2)_{11}$-MgCl			97 ∿ 98	79
ClMgO-$(CH_2)_{11}$-MgCl			82 ∿ 83	56
ClMgO-$(CH_2)_{12}$-MgCl			82 ∿ 84 (85)[b]	86
ClMgO-$(CH_2)_{12}$-MgCl			64 ∿ 65 (64 ∿ 65)[c]	80
ClMgO-$(CH_2)_{12}$-MgCl			60 ∿ 61	60

[a] All reactions were performed on 2 mmol scales using equimolar amounts of the Grignard reagent and lactone. All products were identified by IR and NMR spectra. [b] M. Stoll and A. Rouve, *Helv. Chim. Acta*, 18, 1087 (1935). [c] V. N. Belov, S. G. Polyakova, and V. I. Bazhulina, *Zh. Org. Khim.*, 3, 1397 (1967) [*C. A.*, 68, 29224r (1968)].

in THF at -30 °C using o-phenanthroline as an indicator, then 1.5 equivalent of magnesium turning was added and the resultant suspension was heated under reflux for 2 h. A solution of the ω-metaloxylated Grignard reagent (3) prepared as above was added slowly to a solution of β-propiolactone (4) and 5 mol% of Li_2CuCl_4 in THF at -10 °C. After the mixture was stirred for 1 h at the same temperature, the reaction was quenched with 3N HCl aq solution and ether. The resulting mixture was extracted with ether, and the solvent was evaporated. The residue was solved in methanol and 3N KOH aq solution was added. After removal of methanol, the aqueous solution was washed with ether and acidified with 3N HCl aq solution. Extraction with ether gave pure ω-hydroxycarboxylic acid (1) in a high yield (see Table). ω-Metaloxylated Grignard reagents (3) reacted also with α- or β-methyl substituted β-propiolactone to give the corresponding ω-hydroxycarboxylic acids. In the case of β-methyl-β-propiolactone, the yields decreased, but the reaction with α-methyl-β-propiolactone gave ω-hydroxy-α-methylcarboxylic acids in high yields (see Table).

As mentioned above, the chemo- and regioselective reaction of β-propiolactones with ω-metaloxylated Grignard reagents enable a short step synthesis of ω-hydroxycarboxylic acids in high yields under mild conditions.

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