NOTES Bull. Chem. Soc. Jpn., 56, 345—346 (1983)

One-step Synthesis of Long-chain Aliphatic α,ω-Dicarboxylic Acids Utilizing the Copper-catalyzed Reaction of β-Propiolactone with α,ω-Di-Grignard Reagents

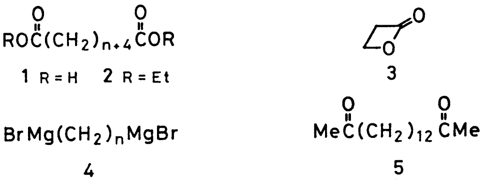
Tamotsu FUJISAWA,* Toshio SATO, Tatsuo KAWARA, and Hideyuki TAGO
Chemistry Department of Resources, Mie University, Tsu, Mie 514

(Received June 28, 1982)

Synopsis. Copper-catalyzed reaction of β-propiolactone with α,ω-di-Grignard reagents, followed by esterification gave six-carbon homologated α,ω-dicarboxylic acid esters in good yields.

Long-chain aliphatic α,ω-dicarboxylic acids or esters are useful synthetic intermediates for many-membered carbon rings. Especially, α,ω-dicarboxylic acids of C_{14}—C_{18} have been used for the syntheses of alicyclic ketones which possess a musk or civet odor.[1)] Although a number of synthetic methods for these acids have been reported,[2—4)] the most direct ones are the Kolbe electrolytic synthesis from half esters of α,ω-dicarboxylic acids[3)] or α-alkylation of carboxylic acids or esters with α,ω-dibromoalkanes.[4)] However, such methods are generally not satisfactory with respect to yield or to availability of starting materials.

Recently the regioselective ring-opening reaction of β-propiolactones with Grignard reagents in the presence of a copper(I) catalyst has been found to give three-carbon homologated carboxylic acids in high yields.[5)] We wish to describe here a novel one-step synthesis of six-carbon homologated α,ω-dicarboxylic acids (**1**) by the reaction of two equivalents of β-propiolactone (**3**) with α,ω-di-Grignard reagents (**4**) in the presence of a copper catalyst.[6)]



Scheme 1.

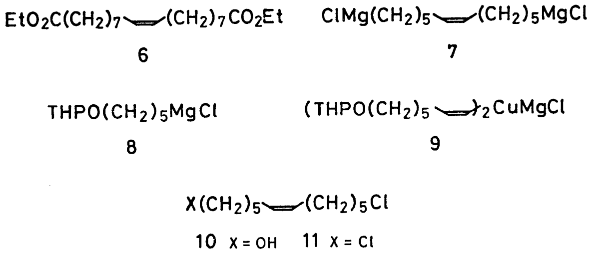
Grignard reagent **4**, easily prepared from α,ω-dibromoalkane,[7)] was added to a solution of two equivalents of **3** and a copper catalyst (2—3 mol%) at −10 °C. After the reaction mixture was allowed to warm to 0 °C and stirred for 3 h, **1** was obtained. As a catalyst, lithium tetrachlorocuprate was slightly superior to copper(I) iodide. Esterification of **1** with ethanol gave diester **2**, which was isolated by distillation. The yields of **2** of C_{14}—C_{18} are listed in Table 1.

Tetradecanedioic acid (**2**, n=8), prepared by the reaction of **3** with 1,8-octanediyldimagnesium dibromide, was easily converted into hexadecane-2,15-dione (**5**), which is a useful precursor for 3-methylcyclopentadecanone (muscone).[8)] The acid was treated with thionyl chloride and then bromomagnesium dimethylcuprate to give **5** in an overall yield of 57% from the Grignard reagent.

TABLE 1. YIELDS OF α,ω-DICARBOXYLIC ACID DIESTERS **2**

Grignard reagent	**2**	Yield/%
$BrMg(CH_2)_8MgBr$	$EtO_2C(CH_2)_{12}CO_2Et$	68
$BrMg(CH_2)_9MgBr$	$EtO_2C(CH_2)_{13}CO_2Et$	63
$BrMg(CH_2)_{10}MgBr$	$EtO_2C(CH_2)_{14}CO_2Et$	60
$BrMg(CH_2)_{11}MgBr$	$EtO_2C(CH_2)_{15}CO_2Et$	68
$BrMg(CH_2)_{12}MgBr$	$EtO_2C(CH_2)_{16}CO_2Et$	62

Diethyl (Z)-9-octadecene-1,18-dioate (**6**), an important precursor for (Z)-9-cycloheptadecenone (civetone)[9)] was easily obtained in 53% yield by the reaction of **3** with di-Grignard reagents **7**. According to the modified procedure of Normant *et al.*,[10)] alkylation of dialkenylcuprate **9**, prepared from Grignard reagent **8**,[11)] copper(I) iodide and acetylene, with 1-chloro-5-iodopentane and deprotection gave chloro alcohol **10** which was converted to **7** *via* α,ω-dichloride **11**.



Scheme 1.

Experimental

The IR spectra were recorded on a Hitachi EPI-G2 spectrometer. The NMR spectra were taken with a Varian A-60 spectrometer in CCl_4 using TMS as an internal standard. Di-Grignard reagent was prepared from α,ω-dibromoalkane in THF.[7)]

General Procedure for the Reaction of β-Propiolactone (3) with α,ω-Di-Grignard Reagents 4. To a solution of Li_2CuCl_4 (3 mmol) and **3** (5.62 g, 78 mmol) in THF (250 ml) was slowly added **4** (30 mmol) at −10 °C and stirred at 0 °C for 3 h. After addition of 3 M† HCl (100 ml), the mixture was extracted with ether and concentrated. The residue was solved in methanol (20 ml) and 3 M KOH (100 ml) was added. After removal of methanol, the solution was washed with ether and acidified with 6 M HCl (100 ml). Extraction with ether and concentration gave crude **1**. Esterification of **1** with ethanol by an azeotropic method and distillation gave pure **2**. Yields and physical data of **2** are as follows: Diethyl tetradecanedioate (yield 68%); bp 144—151 °C/0.4 Torr (lit,[12)] 135—136 °C/0.15 Torr); mp 28.0—29.0 °C (lit,[12)] 27 °C). Diethyl pentadecanedioate (yield 63%); bp 160—161 °C/0.35 Torr (lit,[3b)] 152 °C/0.23 Torr); mp 29.5—30.0 °C (lit,[1a)] 30 °C). Diethyl hexadecanedioate (yield 60%); bp 146—148 °C/0.1 Torr (lit,[3a)] 165 °C/1 Torr); mp 38.0—39.0 °C (lit,[3c)] 39.0 °C). Diethyl heptadecanedioate (yield 68%); bp 153—155 °C/0.15 Torr (lit,[3b)] 162 °C/0.02 Torr); mp 40.0—40.5 °C (lit,[1a)] 40—41 °C). Diethyl octadecanedioate (yield 62%); bp 165—170 °C/0.45

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† 1 M=1 mol dm^{-3}.

Torr (lit,[3a]) 180—190 °C/0.35 Torr; mp 46.0—47.0 °C (lit,[3c]) 47.8—48.4 °C).

*Hexadecane-2,15-dione (**5**).* The crude tetradecanedioic acid (11.43 g), obtained by the reaction of **3** (2.39 g, 33 mmol) with 1,8-octanediyldimagnesium dibromide (10.7 mmol), was added into thionyl chloride (9.84 g, 82 mmol) and stirred at room temp overnight and at 40 °C for 2 h. Excess thionyl chloride was evaporated and the residue was dissolved in 10 ml of THF. To a suspension of bromomagnesium dimethylcuprate, prepared from copper(I) iodide (8.55 g, 45 mmol) and methylmagnesium bromide (90 mmol) in THF (150 ml) and Me_2S (15 ml) at −30 °C for 1.5 h, was added the solution of the acid chloride at −78 °C. After stirring at −78 °C for 30 min, cold sat. NH_4Cl solution was added. Extraction with ether and distillation gave **5** (1.55 g, 57%); bp 152—154 °C/0.25 Torr; mp 82—83 °C (lit,[13]) 83.5—84.5 °C).

*(Z)-12-Chloro-6-dodecen-1-ol (**10**).* To a solution of copper(I) iodide (1.90 g, 10 mmol) in THF (30 ml) and Me_2S (3 ml) was added Grignard reagent **8**[11]) (20 mmol) at −30 °C and stirred for 1 h. After allowing the mixture to warm to −25 °C, acetylene (560 ml) was introduced over a period of 30 min, and stirring was continued at −25—−20 °C for 30 min. Hexamethylphosphoric triamide (4 ml), 1-chloro-5-iodopentane (4.66 g, 20 mmol), and trimethyl phosphite (3.5 ml) were added successively and stirred at room temp overnight. After cooling to 0 °C, 3 M HCl (20 ml) was added. The mixture was extracted with hexane and concentrated. After the residue was heated in methanol (100 ml) in the presence of *p*-toluenesulfonic acid monohydrate (0.2 g) at 50 °C for 3 h, sat. $NaHCO_3$ solution (50 ml) was added. Extraction with hexane and distillation gave **10** (2.7 g, 63%); bp 116—120 °C/0.35 Torr; NMR δ 1.1—2.3 (16H), 3.13 (1H, s), 3.48 (2H, t, J=7 Hz), 3.52 (2H, t, J=7 Hz), 5.29 (2H, t, J=5 Hz); IR (neat) 3400 (OH) and 720 cm^{-1} (*cis*-CH=CH). Found: C, 65.90; H, 10.45; Cl, 16.06%. Calcd for $C_{12}H_{23}ClO$: C, 65.88; H, 10.60; Cl, 16.21%.

*(Z)-1,12-Dichloro-6-dodecene (**11**).* Chloro alcohol **10** (2.99 g, 13.7 mmol) and triphenylphosphine (9.40 g, 40 mmol) were refluxed in CCl_4 (28 ml) for 1 h. After addition of dry hexane (14 ml), the white precipitate was filtered off. Concentration and distillation gave **11** (2.13 g, 66%); bp 106—108 °C/0.3 Torr; NMR δ 1.5—2.2 (16H), 3.51 (4H, t, J=6 Hz), 5.30 (2H, t, J=4 Hz); IR (neat) 720 cm^{-1} (*cis*-CH=CH). Found: C, 60.56; H, 9.54; Cl, 29.61%. Calcd for $C_{12}H_{22}Cl_2$: C, 60.76; H, 9.35; Cl, 29.89%.

*Diethyl (Z)-9-Octadecene-1,18-dioate (**6**).* Grignard reagent **7** was prepared in 79% yield from **11** (2.11 g, 8.91 mmol) and magnesium in THF (23 ml) under reflux for 2 h. Diester **6** was prepared from **3** and **7**. Purification by TLC on silica gel (R_f 0.4, hexane:ether=5:1) gave **6** (1.19 g, 50%); bp 156—160 °C/0.3 Torr; NMR δ 1.23 (6H, t, J=7 Hz), 1.30—2.1 (24H), 2.20 (4H, t, J=7 Hz), 4.05 (4H, q, J=7 Hz), 5.33 (2H, t, J=4 Hz); IR (neat) 1725 (C=O) and 720 cm^{-1} (*cis*-CH=CH). Found: C, 71.80; H, 10.76%. Calcd for $C_{22}H_{40}O_4$: C, 71.69; H, 10.94%.

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