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SYNTHESIS OF γ-KETOPIMELIC ACID DERIVATIVES BY RHODIUM CARBONYL-CATALYZED HYDROCARBONYLATION OF ACRYLIC ACID DERIVATIVES

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The rhodium carbonyl-catalyzed reactions of acrylic acid derivatives (1) with CO in *iso*-propanol gave selectively γ-ketopimelic acid derivatives (2) in good yields. In the reaction of ethyl acrylate (1b) in *iso*-propanol-d_8, deuterium scrambling in the methylene groups of the product (2b) was observed.

In a previous paper we have reported that 5-alkyl-3,4-disubstituted-2(5H)-furanones are formed by the rhodium carbonyl-catalyzed reactions of internal acetylenes with olefins and CO in hydrogen donating solvents such as alcohol and aqueous acetone.[1)] When methyl acrylate (1a) was used as an olefin in the reaction, dimethyl γ-ketopimelate (2a) was detected as a by-product. The γ-ketopimelate (dimethyl 4-oxoheptanedioate) would be formed by the hydrocarbonylation of 1a with CO and hydrogen donor,[2)] and we took an interest in its selective formation among the three possible hydrocarbonylation products; 2a, dimethyl 2-methyl-3-oxohexanedioate (3a), and dimethyl 2,4-dimethyl-3-oxopentanedioate (4a). In this paper we wish to report a convenient synthetic method of γ-ketopimelic acid derivatives by the hydrocarbonylation of acrylic acid derivatives with CO in *iso*-propanol. The general synthesis can be expressed by the following equation.

$$\underset{\underline{1}}{2\ CH_2{=}CHCOY} + CO + (CH_3)_2CHOH \longrightarrow \underset{\underline{2}}{OC(CH_2CH_2COY)_2} + (CH_3)_2CO$$

Y= OMe, OEt, OBu, $OCH_2CH(Et)Bu$, and NMe_2

In a typical experiment, carbon monoxide (75 Kg/cm^2) was introduced into a stainless steel autoclave containing ethyl acrylate (1b, 100 mmol), $Rh_4(CO)_{12}$ (0.025

mmol), and *iso*-propanol (300 mmol), and the autoclave was heated at 180°C for 6 h. The reaction mixture was analyzed by GLC, observing the recovery of 1b (13.1 mmol) and the formation of diethyl γ-ketopimelate (2b, 24.6 mmol, 57% yield based on 1b consumed), ethyl propionate (5b, 12.7 mmol, 15%), and acetone (30.9 mmol). The product 2b (bp 129-131 °C/1 mmHg, lit.3) 116-121 °C/0.3 mmHg) could be isolated in a 47% yield by vacuum distillation of the reaction mixture, and was identified by its IR, NMR, and mass spectra. The formation of acetone shows *iso*-propanol to act as a hydrogen donor. The results of the hydrocarbonylation of 1b carried out under several conditions (Table 1) showed that the yield of 2b depends both on the reaction temperature and the ratio of 1b to hydrogen donor, as well as on the type of alcohol used as hydrogen donor (*i*-PrOH > EtOH, compare run no.7 with run no.2), but is not influenced so much by pressure of CO. Ethyl propionate (5b) was found in a large amount when a large excess of hydrogen donor was present. In this reaction the formation of the hydroformylation product, ethyl formylpropionate, and of the hydroesterification product, dialkyl succinate, were very small ($\leq$ 1%) and the polymerization of some part of 1b (10-20%) was observed.

Similarly, the reactions of methyl, butyl, and 2-ethylhexyl acrylates (1a, 1c, and 1d) produced the corresponding dialkyl γ-ketopimelates (2a, 2c, and 2d) in good yields. Acrylic acid (1e) gave no γ-ketopimelic acid (2e), but diethyl ketone by the decarboxylation of 2e. N,N-Dimethylacrylamide (1f) also gave bis(N,N-dimethyl)-γ-ketopimelamide (2f), whereas acrylamide and N-phenylacrylamide gave no γ-ketopimelamide, probably due to the interaction of the N-H bond with the catalyst. These results were summarized in Table 2.

It is noteworthy that the hydrocarbonylation of 1 produces selectively 2 (at least in 98% selectivity)4) among the three possible products, 2, 3, and 4, whereas propylene gives a mixture of three isomeric ketones in a statistical ratio.5) We examined the reaction of 1b in *iso*-propanol-d_8 in order to explore the reaction course. The hydrogen distribution in 2b obtained by the experiment was $OC(CH_{1.3}D_{0.7}CH_{1.7}D_{0.3}CO_2CH_2CH_3)_2$ from its ^1H NMR spectrum,6) and the isotopic composition inferred from mass spectroscopy was 5.8 (d_0), 31.6 (d_1), 31.1 (d_2), 18.0 (d_3), 8.2 (d_4), 3.5 (d_5), 1.4 (d_6), and 0.5% (d_7).7) These results indicate the scrambling of deuterium atoms in the product. In a reaction carried out by heating a mixture of 2b-d_0, $Rh_4(CO)_{12}$, and *iso*-propanol-d_8 under similar conditions, 2b was recovered and unchanged. Since no deuterium incorporation was detected in the recovered

Table 1. The Hydrocarbonylation of Ethyl Acrylate (1b) under Several Conditions[a]

Run No.	ROH	Molar ratio (1b / ROH)	CO (Kg/cm^2)	Temp/Time (°C/ hrs)	Conversion (%)	Products (%)[b] 2b	5b
1	EtOH[d]	1 / 8.5	50	150 / 7	29	52	tr.
2	EtOH	1 / 8.5	50	180 / 9	100	35	50
3	EtOH	1 / 8.5	50	200 / 7	100	26	56
4	*i*-PrOH	1 / 3	50	180 / 6	91	53	20
5	*i*-PrOH	1 / 3[c]	50	180 / 6	80	44	30
6	*i*-PrOH	1 / 6.5	50	180 / 6	98	46	42
7	*i*-PrOH	1 / 10	50	180 / 6	95	42	43
8	*i*-PrOH	1 / 3	75	180 / 6	87	57	15
9	*i*-PrOH	1 / 3	95	180 / 6	87	60	14

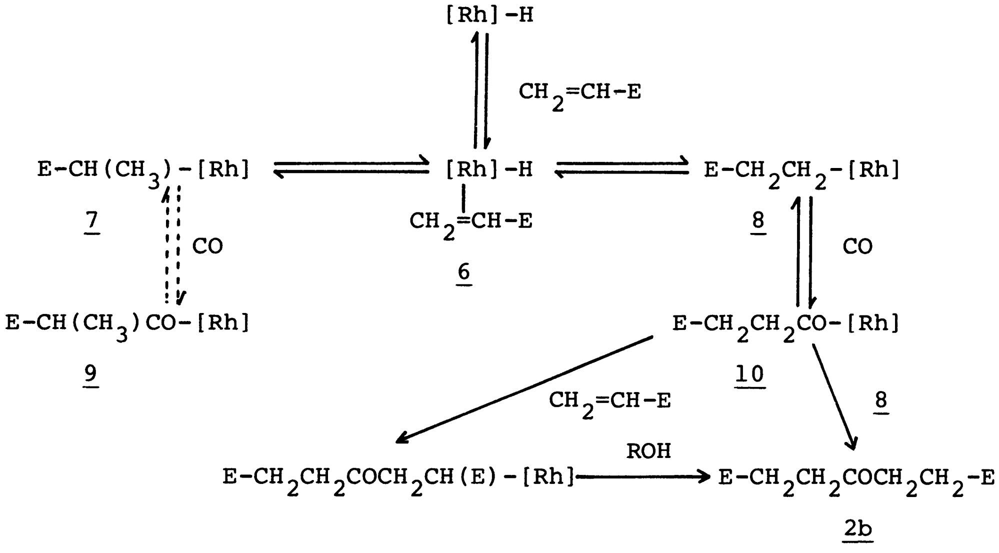
a) Ethyl acrylate (100 mmol) and Rh$_4$(CO)$_{12}$ (0.025 mmol) were used. b) The yields were based on 1b consumed and were determined by GLC. c) Diluted with acetone (700 mmol). d) Using ethanol as hydrogen donor, acetaldehyde diethyl acetal was formed.

Table 2. The Hydrocarbonylation of Acrylic Acid Derivatives (1)[a]

CH$_2$=CHCOY 1 (Y)	Conversion (%)	Products (%)[b] 2	5	2 / Rh (mol / g atom)
1a (OMe)	n.d.[c]	38[c]	n.d.	189
1b (OEt)	87	57	15	246
1c (OBu)	90	51	15	230
1d (OCH$_2$CH(Et)Bu)	86	53	14	229
1f (NMe$_2$)	94	47	31	219

a) Reaction conditions; 1, 100 mmol; Rh$_4$(CO)$_{12}$, 0.025 mmol; *i*-PrOH, 300 mmol; CO, 75 Kg/cm^2; 180°C, 6 h. b) The yields were based on 1 consumed and were determined by GLC. c) Not determined. The yield of 2a was based on 1a used.

2b, the scrambling must take place during the hydrocarbonylation of 1b, and we consider that the scrambling would occur through a sequence of addition and elimination reactions involving the olefin and [Rh]-H arising from the catalyst and *iso*-propanol, as shown in Scheme. Although α- and β-ethoxycarbonylpropyl complexes (7 and 8) are present in the reaction, as shown by the deuterium scrambling, the intermediate 8 plays apparently an important part in the subsequent reactions for the selective formation of 2b; thus, the insertion of CO into 8 gives an acyl complex 10, which reacts with 8, or adds to 1, followed by reductive elimination, to give 2b. In the hydroformylation of 1b with cobalt[8] and rhodium carbonyls,[9] the ratio of ethyl 3-formylpropionate to ethyl 2-formylpropionate increases with an increase in the reaction temperature. This effect has been explained by the rapid isomerization of α-ethoxycarbonylpropionyl complex to β-ethoxycarbonylpropionyl complex corresponding to 9 and 10, respectively, at a relatively high temperature.[10] Our present results indicate the presence of an interconversion between α- and β-ethoxycarbonylpropyl complexes (7 and 8) and the ease of insertion of CO into 8 to form 10.



Scheme (E= CO_2Et)

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4) By GC/MS the compound corresponding to 3 or 4 could be detected, but the amount was about 2% of 2.
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6) The 400 MHz ^{1}H-NMR spectrum of 2b reveals two triplets at δ2.79 and 2.59 due to β- and α-methylenes. We assign tentatively the resonance at a lower magnetic field to β-methylene adjacent to the carbonyl group on the basis of data of $\underline{CH_3}$COEt (δ2.13), $\underline{CH_3}CO_2$Et (δ2.03) and levulinic acid.[11] The hydrogen distribution was calculated on the assumption that the number of hydrogen atoms in -O$\underline{CH_2}$- is 2.0.
7) The isotopic composition was calculated from the peak at m/e 185 (M^+-OEt), because the parent ion peak (M^+ 230) was very small.
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