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Carboxymethylation of Organic Halides by Palladium Complexes under Mild Conditions[1)]

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Palladium complexes, $Pd(CO)(PPh_3)_3$, $Pd_3(CO)_3(PPh_3)_4$, $Pd_3(CO)_3(PPh_3)_3$, and $PdCl_2(PPh_3)_2$ were found to be excellent catalysts for the carboxymethylation of various organic halides under very mild conditions. The carboxymethylation reaction is considered to proceed *via* acyl complexes as the intermediates.

In previous papers we reported syntheses of palladium(0) carbonyl complexes, $Pd(CO)(PPh_3)_3$ (**1**), $Pd_3(CO)_3(PPh_3)_4$ (**2**), and $Pd_3(CO)_3(PPh_3)_3$ (**3**),[2)] and the oxidative addition of various organic halides to **1** affording acyl complexes of palladium.[3)] In the present paper is described carboxymethylation of various organic halides under ambient conditions catalyzed by **1**, **2**, **3**, and also $PdCl_2(PPh_3)_2$ (**4**).

A number of papers on the carbonylation of organic halides by transition metal complexes have been reported, but the reactions required high temperature and pressure. Recently there appeared several reports on the carbonylation of organic halides under ambient conditions, in which $Ni(CO)_4$,[4—7)] $NaCo(CO)_4$,[8)] or a nickel-thiourea complex[9)] was used as the catalyst in combination with base. However, the yields of carbonylated products were below one mole or at best a few mole per mole of the transition metal complex used, and reaction temperatures of *ca.* 100° were sometimes required. In contrast, the palladium complexes **1**—**4** show remarkable catalytic activities in the carboxymethylation of various organic halides under very mild conditions.

Results and Discussion

When carbon monoxide is bubbled through a mixture of iodobenzene, methanol, diethylamine, and the palladium(0) complex (**1**, **2**, or **3**) at room temperature, methyl benzoate is produced with the formation of diethylammonium iodide. The yield of the ester was determined by means of gas chromatography and observed to increase linearly with the reaction time. Table 1 shows the yields exceeding far 100% based on palladium atom, along with other results which will be described hereinafter. As shown in Table 1, catalytic activities of **2** and **3** are comparable and higher than that of **1**.

Since **1** and **2** are formed by the treatment of **4** with methanol, diethylamine, and carbon monoxide,[10)] **4** can be conveniently used as the catalyst for the carboxymethylation instead of **1**, **2**, or **3**. Complex **4** is a stable compound and easy to handle compared with **1**, **2**, and **3** which are appreciably air-sensitive. Therefore carboxymethylation of various organic halides was carried out by employing **4** as the catalyst, and the

Table 1. Catalytic carboxymethylation of organic halides by palladium complexes

$$RX \xrightarrow[\text{CO, MeOH, Et}_2\text{NH}]{\text{Pd Complex}} RCOOMe + Et_2NH\cdot HX$$

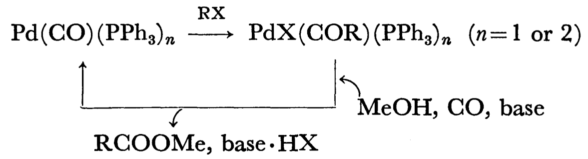
Complex	Halide	Temp. °C	CO Press. atm	Time hr	Yield of methyl ester mol/Pd	
1[a)]	Iodobenzene	18	1	5	Benzoate	6.0
2[a)]	Iodobenzene	18	1	5	Benzoate	10.0
3[a)]	Iodobenzene	18	1	5	Benzoate	10.0
4[a)]	Iodobenzene	18	1	5	Benzoate	9.5
5[a)]	Iodobenzene	18	1	5	Benzoate	9.0
6[a)]	Iodobenzene	18	1	5	Benzoate	13.5
1+PPh_3[a,d)]	Iodobenzene	18	1	5	Benzoate	2.7
4+PPh_3[a,d)]	Iodobenzene	18	1	5	Benzoate	5.0
4[b)]	*p*-Iodotoluene	24	1	5	*p*-Toluate	18.3
4[b)]	Bromobenzene	50	1	6	Benzoate	8.8
4[b)]	Bromobenzene	100	45	10	Benzoate	57.0
4[b)]	*p*-Dibromobenzene	80	10	1	*p*-Bromobenzoate Terephthalate	17.8 12.0
4[b)]	*β*-Bromostyrene	24	1	11	Cinnamate	21.3
4[b)]	1-Bromo-2-ethoxyethylene	50	1	2.5	*β*-Ethoxyacrylate	1.4
1[c)]	Benzyl Bromide	19	1	3	Phenylacetate	13.5
1[c)]	Methyl Iodide	20	1	3	Acetate	trace

a) Molar ratio of the complex: iodobenzene: diethylamine: methanol is 0.01: 1: 1: 5. In case of **2** or **3**, the molecular weight is reduced to a mononuclear basis. b) Molar ratio of the complex: halide: diethylamine is 0.01 to 0.02 : 1: 1. c) Calcium oxide is used as the base in place of diethylamine. Molar ratio of **1**: halide: CaO: methanol is 0.01: 0.8: 0.2: 10. d) One molar equivalent of PPh_3 is added.

results are listed also in Table 1. The reaction procedure is essentially the same as in the case of **1**, **2**, or **3**. The methyl esters are formed after an induction period of about 30 min, and the yields increase linearly with the reaction time even after 22 hr. As shown in Table 1, iodobenzene, *p*-iodotoluene, bromobenzene, *p*-dibromobenzene, *β*-bromostyrene, and 1-bromo-2-ethoxyethylene are converted catalytically by **4** to corresponding esters in high yields under mild conditions. Organic halides such as vinyl chloride, vinyl bromide, 1,2-dichloroethylene, 1,2-dibromoethylene, and chlorobenzene did not afford corresponding esters under the same conditions.

Amines other than diethylamine, *e.g.* dicyclohexylamine, can be used as the base. Organic halides that readily form ammonium salts with amines cannot be used as the substrate. But the use of calcium oxide as the base in place of amines enables carboxymethylation of benzyl bromide as well as iodobenzene at room temperature and under 1 atm carbon monoxide. As indicated in the lowest lines of Table 1, benzyl bromide was converted catalytically to methyl phenylacetate by **1**, while methyl iodide gave only a trace amount of methyl acetate.

In order to elucidate the reaction mechanism, two kinds of benzoyl complexes of palladium were also employed as the catalyst for the carboxymethylation of iodobenzene. One is $PdI(COPh)(PPh_3)_2$ (**5**), which is obtained by the reaction of **1** with iodobenzene in toluene under carbon monoxide at room temperature, and has an IR absorption at 1634 cm^{-1} assignable to $\nu_{O=O}$.[3] The other one is $[PdI(COPh)(PPh_3)\cdot toluene]$ (**6**), which is obtained by the reaction of **2** or **3** with iodobenzene in toluene (in the reaction of **2**, **6** is obtained together with **5**), and has an absorption at 1660 cm^{-1} also assignable to $\nu_{C=O}$. Both of **5** and **6** give molar equivalent of methyl benzoate by the treatment with methanol and diethylamine under nitrogen at room temperature. Moreover, they show similar catalytic activities in the carboxymethylation of iodobenzene as shown in Table 1. These results suggest that the benzoyl complexes **5** and **6** are the reaction intermediates of the carboxymethylation, and the following scheme is proposed.[11]



In the absence of base, the palladium complexes show no catalytic activities. That is, when carbon monoxide is bubbled through a mixture of **1**, iodobenzene, and methanol for several hours, no ester formation is observed. And when diethylamine is added to the mixture after carbon monoxide is expelled by nitrogen bubbling, stoichiometric amount of benzoate is obtained. This indicates the reductive elimination of benzoyl iodide hardly occurs in the absence of base. Therefore the base is considered to rather enhance the direct attack of methoxide anion on the Pd-COPh moiety than neutralize the acidity being formed during the reaction. The acidity constant of methanol is 10^{-16}, while the equilibrium constant of $MeOH + R_2NH \leftrightarrows MeO^- + R_2NH_2^+$ is about 10^{-6}.[12]

As shown in Table 1, the yield of methyl benzoate from iodobenzene depends on the palladium complexes used and increases in the order **1**<**4**<**2**—**3**. When one molar equivalent of triphenylphosphine is added to the reaction mixture catalyzed by **4**, the yield observed is similar to that with **1**. This is compatible with the fact that **1** is prepared by treatment of **4** with diethylamine and methanol in the presence of one molar equivalent of triphenylphosphine under carbon monoxide. The addition of triphenylphosphine to **1** lowers the yield of ester formation since the ligand added shifts the equilibrium $\mathbf{1} \leftrightarrows Pd(CO)(PPh_3)_2 + PPh_3$ to the left-hand side and prevents the oxidative addition of iodobenzene.[3]

Experimental

Syntheses of complexes **1**, **2**, **3**, and **5** were already described in previous papers.[2,3,10] The complex **1** was also prepared by treatment of **4** with diethylamine and methanol in the presence of one molar equivalent of triphenylphosphine under carbon monoxide (yield, 60%). These complexes are air-sensitive and their handling must be conducted in oxygen-free, dry atmosphere. Complex **4** was prepared according to the published method.[14] Methanol, toluene, and diethylamine were purified according to the usual methods and distilled under nitrogen atmosphere. Organic halides were commercially obtained and were degassed and saturated with carbon monoxide before use. 1-Bromo-2-ethoxyethylene was prepared according to the published method.[15] Esters used as the standard material in gas chromatography analyses were commercially obtained.

Carboxymethylation Reaction under 1 atm Carbon Monoxide. When carbon monoxide was bubbled at room temperature (18°C) through a stirred mixture of **1** (0.100 g, 0.109 mmol), iodo benzene (2.22 g, 10.9 mmol), methanol (1.76 g, 55.0 mmol), and diethylamine (0.80 g, 11.0 mmol), the mixture became a yellow, homogeneous solution and then white powder of ammonium salt precipitated gradually with the formation of benzoate. After 5 hr the amount of benzoate determined by gas chromatography was 0.65 mmole (6.0 times molar equivalent of **1**). The above procedure was applied to all other similar reactions.

Another reaction system containing **4** (0.100 g, 0.285 mmole), iodobenzene (5.50 g, 27.0 mmole), dicyclohexylamine (3 ml), and methanol (5 ml) afforded methyl benzoate of 15.7 times molar equivalent of **4** for 6.5 hr, and 48.6 times for 22 hr at room temperature. Still other system containing **1** (0.100 g, 0.109 mmol), benzyl bromide (1.44 g, 8.42 mmol), calcium oxide (0.100 g, 1.78 mmol), and methanol (3.95 g, 123 mmol) gave methyl phenylacetate of 1.47 mmol (13.5 times molar equivalent of **1**) for 3 hr at 19 °.

Carboxymethylation under Elevated Pressures. In a 50 ml stainless-steel autoclave were placed **4** (0.200 g, 0.285 mmol), *p*-dibromobenzene (6.37 g, 27.0 mmol), methanol (20 ml), and diethylamine (3 ml). The reaction mixture was magnetically stirred at 80 °C under carbon monoxide pressure of 10 kg/cm^2, and 1 hr after the pressure dropped to zero. The mixture was extracted by 100 ml of toluene, in which methyl *p*-bromobenzoate (5.13 mmol), dimethyl terephthalate (3.46 mmol), and unreacted *p*-dibromobenzene (18.4 mmol) were analyzed.

Preparation of [*PdI (COPh) (PPh*$_3$*)·toluene*] (*6*). When carbon monoxide was bubbled through a toluene solution (10 ml) of **2** (0.173 g, 0.126 mmol) and iodobenzene (3 ml), the original red color of the solution turned into yellow in 15 min. After the solution was allowed to stand overnight, yellow crystals of **6** precipitated (0.148 g (55% based on Pd), $\nu_{C=O}$ at 1660 cm^{-1}). Cryoscopic molecular weight measurement could not be conducted because of the insufficient solubility of the complex. Found: C, 54.99; H, 4.00; P, 4.88%. Calcd for $C_{32}H_{28}OPIPd$: C, 55.50; H, 4.04; P, 4.48%. By adding *n*-hexane to the filtrate of the above solution, yellow crystals of **5** precipitated (0.050 g (16% based on Pd), $\nu_{C=O}$ at 1634 cm^{-1}). When the reaction was carried out in methanol in place of toluene, was obtained yellow powder which was a mixture of **5** and **6**.

Stoichiometric Ester Formation from 5 or 6. When the benzoyl complex **5** (0.119 g) was treated with methanol (2.5 ml) and diethylamine (1.5 ml) under nitrogen at room temperature, the original yellow color turned into brown, and 99.9% molar equivalent of methyl benzoate resulted. As for **6**, the procedure was almost the same.

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13) The complex **4** affords a mixture of **1** and **2** by the treatment with carbon monoxide, methanol, and diethylamine, while in the presence of one molar equivalent of triphenylphosphine **4** is converted to **1** exclusively.

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