Palladium(II) Complex-catalysed Formation of α-Keto Acids *via* Double Carbonylation of Organic Halides

Masato Tanaka,* Toshi-aki Kobayashi, and Toshiyasu Sakakura

National Chemical Laboratory for Industry, Yatabe, Tsukuba, Ibaraki 305, Japan

Organic halides are doubly carbonylated in the presence of water using the $PdCl_2(PPh_3)_2$ catalyst leading to the formation of α-keto acids.

Metal complex-catalysed carbonylation of organic halides is a useful and industrially important reaction. Normally, a halide molecule reacts with one molecule of carbon monoxide to form carboxylic acids or derivatives, *e.g.* esters, amides, and aldehydes [equation (1)].[1] During our studies on ketone synthesis *via* halide carbonylation,[2] we observed the first successful double carbonylation leading to the formation of α-keto amides.[3] Since it expands the scope of carbonylation, the double carbonylation of halides is of interest for the direct synthesis of α-keto acid derivatives which are useful intermediates for, *e.g.*, α-amino acids, but examples are still rare.[4] We now report the first example of palladium complex-catalysed double carbonylation of organic halides which affords α-keto acids.

$$R^1X + CO + HY + NR^2_3 \longrightarrow R^1COY + NR^2_3HX \qquad (1)$$

$$(Y = OH, OR^3, NR^3_2, H)$$

$$PhI + 2CO + H_2O + NEt_3 \xrightarrow{-NHEt_3I} PhCOCO_2H \xrightarrow{CH_2N_2} \underset{(\mathbf{1})}{PhCOCO_2Me} \qquad (2)$$

Treatment of iodobenzene with water, triethylamine, and a catalytic amount of $PdCl_2(PPh_3)_2$ under carbon monoxide gave benzoylformic acid. The acid itself could be isolated, but was conveniently transformed by methylation with diazomethane into the methyl ester (**1**) [equation (2)] which was identified by spectroscopic comparison [^1H n.m.r. δ ($CDCl_3$) 7.4—8.3 (Ph) and 3.97 (Me); $\nu_{max.}$ (neat) 1687 (CO) and 1735 cm^{-1} (CO_2Me)] with an authentic sample prepared by a different route. Methyl benzoate and benzaldehyde were also formed as by-products. Other aromatic and heterocyclic halides also underwent the double carbonylation in a similar manner.† Preliminary results, without optimization, are summarized in Table 1.

Based on mechanistic investigations for α-keto amide synthesis,[5] the present reaction is also expected to proceed through the formation of the benzoyl-carboxy-palladium complex (**2**) (Scheme 1) as the key intermediate which collapses *via* reductive elimination into the keto acid. Benzoylformic acid is not an intermediate for benzaldehyde formation, since under the carbonylation conditions (150 atm, 60 °C, 40 h, palladium complex, water, and triethylamine) it

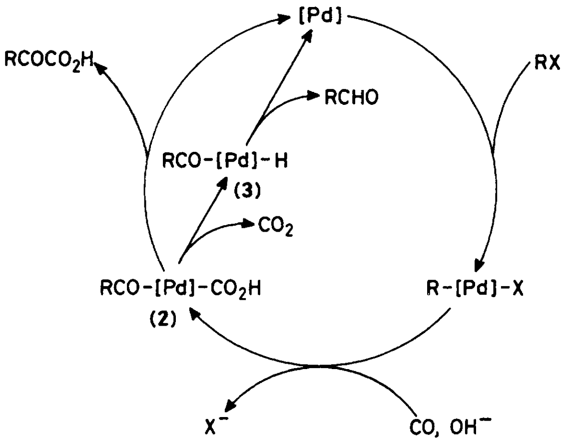
---

† A typical procedure is as follows. A 50 ml stainless steel autoclave, charged with iodobenzene (4 mmol), water (1 ml), triethylamine (5 ml), and dichlorobis(triphenylphosphine)palladium (0.038 mmol), was pressurized with carbon monoxide to 150 atm (at room temperature), and was then heated at 60 °C for 36 h. The resulting mixture was poured into ether–water (1:1). G.l.c. analysis of the ether layer showed the formation of benzaldehyde (52 mg). The aqueous layer was acidified with hydrochloric acid, and was extracted with ether. Methylation with diazomethane, prepared from *N*-nitrosomethylurea and potassium hydroxide, preparative t.l.c. (silica gel; hexane–ether, 5:1) and short-path distillation [b.p. 135—141 °C (bath temp.) at 15 Torr] led to the isolation of the pure keto acid methyl ester (249 mg).

Table 1. Carbonylation of halides in the presence of water.

Halide RX	P(CO)/ atm	Temp./ °C	Time/ h	Conversion[a] (%)	Yield (%)[b] RCOCO$_2$H	RCO$_2$H	RCHO
PhI	150	60	36	93.1	43.3	17.2	13.4
PhI	150	40	72	70.1	53.1	6.3	16.3
p-MeC$_6$H$_4$I	150	60	48	86.5	40.5	17.3	15.6
C$_4$H$_3$SI[c]	150	80	10	100	47.1	24.1	13.5
PhBr	30	100	96	41.9	3.0	69.5	13.6

[a] Conversion refers to consumption of the halides. [b] Analysed by g.l.c. and based on the amount of consumed halide. Yields of acids were estimated after methylation with diazomethane. [c] 2-Iodothiophene.



Scheme 1

was recovered nearly quantitatively in a separate experiment. An alternative route to benzaldehyde could be the reduction of a benzoyl complex with molecular hydrogen which could possibly be formed by the water gas shift reaction. However, hydrogen could not be detected. *trans*-β-Iodostyrene, which was selectively carbonylated to form cinnamic acid and did not undergo the double carbonylation, did not give cinnamaldehyde either. Therefore, benzaldehyde formation might be rationalized by the decarboxylation of the complex (**2**) to give the hydrido complex (**3**) prior to the reductive elimination process.

Received, 25th January 1985; Com. 109

References

1 A. Schoenberg and R. F. Heck, *J. Am. Chem. Soc.*, 1974, **96**, 7761; A. Schoenberg, I. Bartoletti, and R. F. Heck, *J. Org. Chem.*, 1974, **39**, 3318; A. Schoenberg and R. F. Heck, *ibid.*, 1974, **39**, 3327; J. K. Stille and P. K. Wong, *ibid.*, 1975, **40**, 532; M. Hidai, T. Hikita, Y. Wada, Y. Fujikura, and Y. Uchida, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 2075; L. Cassar, M. Foa, and A. Gardano, *J. Organomet. Chem.*, 1976, **121**, C55.

2 T. Kobayashi and M. Tanaka, *J. Chem. Soc., Chem. Commun.*, 1981, 333, and references cited therein.

3 T. Kobayashi and M. Tanaka, *J. Organomet. Chem.*, 1982, **233**, C64.

4 B. Fell and H. Chrobaczek, *Chem.-Ztg.*, 1984, **108**, 291, and references cited therein.

5 J.-T. Chen and A. Sen, *J. Am. Chem. Soc.*, 1984, **106**, 1506; F. Ozawa, T. Sugimoto, Y. Yuasa, M. Santra, T. Yamamoto, and A. Yamamoto, *Organometallics*, 1984, **3**, 683; F. Ozawa, T. Sugimoto, T. Yamamoto, and A. Yamamoto, *ibid.*, 1984, **3**, 692.