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Palladium-Catalyzed Carbonylation of Aromatic Aldehydes and Hydrocarbons. A Novel Synthetic Route to α-Keto Amides via C-H Activation

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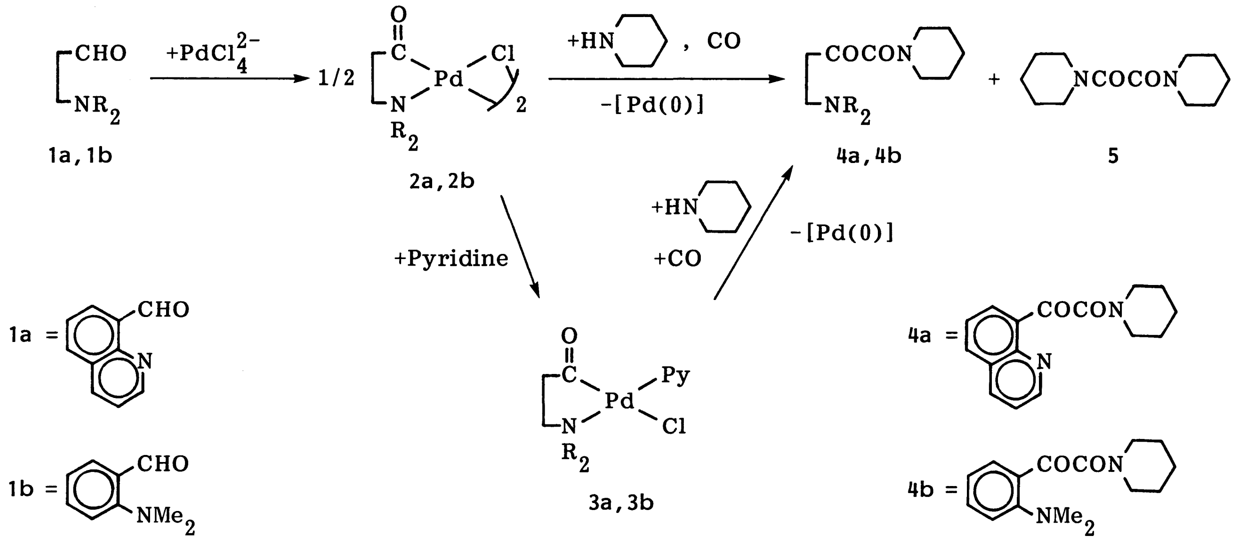
Aromatic aldehydes (ArCHO: quinoline-8-carbaldehyde and o-(N,N-dimethylamino)benzaldehyde) react with tertachloropalladate(II) through a C-H activation reaction to give the corresponding aroylpalladium complexes, which afford α-keto amides $(\mathrm{ArCOCO\overline{N(CH_2)_4C}H_2})$ in high yields upon carbonylation with piperidine. Attempts for double carbonylation through orthopalladation reactions of aromatic hydrocarbons are also reported.

The recently developed double carbonylation reactions have provided convenient synthetic routes to α-keto acid derivatives.[1)] The double carbonylation reactions of organic halides have been extensively studied and various aryl and alkenyl halides are converted into α-keto acid derivatives in good to modest yields under appropriate conditions. In contrast, the double carbonylation of organic compounds other than halides is still limited.[2)] Since α-keto acids are known to be useful starting materials in organic synthesis,[3)] it is desirable to develop the double carbonylation reactions of a wide variety of organic compounds. The previous studies on the mechanism of the palladium-catalyzed double carbonylation of aryl halides and amines to give α-keto amides have revealed that the reaction proceeds through a mechanism involving aryl- and aroylpalladium intermediates.[4)] This finding has prompted us to study carbonylation reactions of aryl- and aroylpalladium compounds prepared by palladation of aromatic hydrocarbons and aldehydes through C-H activation reactions.[5)] We describe here that such organopalladium species can be utilized as intermediates in the double carbonylation of aromatic compounds to give α-keto amides.[6)]

Quinoline-8-carbaldehyde (**1a**) and o-(N,N-dimethylamino)benzaldehyde (**1b**) can be converted into the corresponding α-keto amides by the sequence of reactions illustrated in Scheme 1. The aroylpalladium complex of structure **2a** was prepared by the reaction of Na_2PdCl_4 and **1a** in ethanol according to the procedure reported by Pregosin.[7)] The reaction requires two equivalents of **1a** relative to palladium because of production of HCl that reacts with **1a** to make a quinolinium chloride. In the presence of sodium bicarbonate (2 equiv./Pd), on the other hand, the HCl generated in the system is effectively trapped and complex **2a** can be obtained over 70% yield starting from one equivalent of **1a**.[8)] Complex **2a** is sparingly soluble



Scheme 1.

in common organic solvents and could not be isolated as an analytically pure crystalline compound. Treatment of **2a** with pyridine in benzene affords the pyridine-coordinated mononuclear complex **3a**, which could been isolated as yellow needles by recrystallization from hot benzene (59%/Na$_2$PdCl$_4$).[9] Similar reaction of **1b** and Li$_2$PdCl$_4$ in methanol or ethanol gives aroylpalladium complex **2b**,[7] which is converted into **3b** on its reaction with pyridine.[10] The reaction of **1b** and Li$_2$PdCl$_4$ proceeds more slowly than that of **1a** and it takes 4 days at room temperature to obtain **2b** over 70% yield.

The aroylpalladium complexes react with piperidine under CO pressure in the presence or absence of Et$_3$N to give α-keto amides **4a** and **4b** together with a small amount of oxamide **5**. Table 1 summarizes the results of the reactions with the pyridine-coordinated complexes **3a** and **3b**. The binuclear complexes **2a** and **2b** gave similar results. Formation of the corresponding amides is negligible in every run. Removal of air from the reaction system is important to achieve clean

Table 1. Reaction of **3a** and **3b** with piperidine under CO pressure[a]

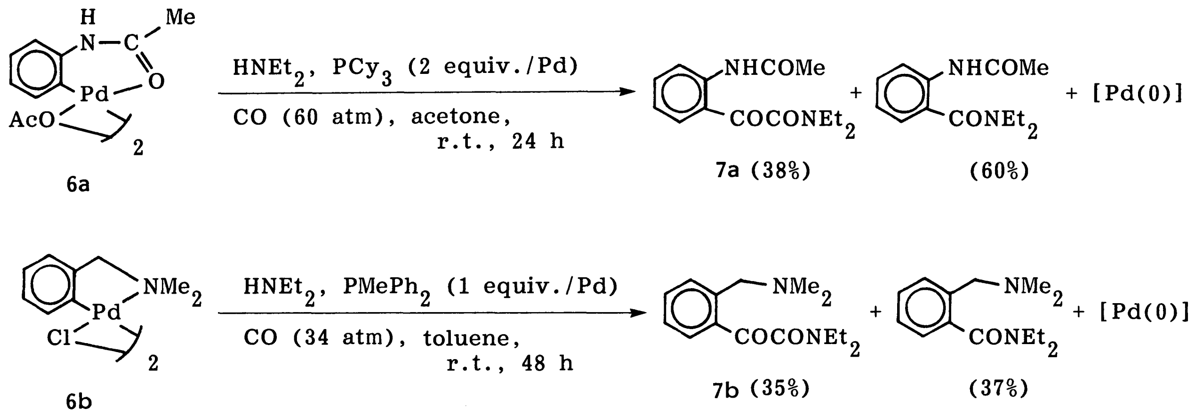
Run	Complex	CO (atm)[b]	Piperidine (cm^3)	Et$_3$N (cm^3)	Temp °C	Time h	Yield/% on Pd[c] 4	5
1	**3a**	70	1	0	70	24	93	6
2[d]	**3a**	80	1	0	70	40	74	60
3[d,e]	**3a**	80	1	0	70	40	59	69
4	**3b**	50	1	0	r.t.	35	100	8
5	**3b**	50	0.1	1	r.t.	15	98	0
6	**3b**	30	0.1	1	r.t.	15	81	0
7	**3b**	10	0.1	1	r.t.	15	7	0

a) Reactions were carried out using the acylpalladium complexes (**3a** = 0.1 mmol, **3b** = 0.05 mmol) in benzene (3 cm^3). b) 1 atm = 101325 Pa. c) Determined by means of GLC. d) Air (1 atm) was added. e) Reaction was carried out in EtOH (3 cm^3).

α-keto amide synthesis; otherwise a considerable amount of oxamide is formed (runs 2 and 3).

The stoichiometric conversion of **1a** and **1b** into the α-keto amides can be performed without isolation of the aroylpalladium complexes. A typical example is as follows: a heterogeneous mixture of **1a** (0.1 mmol), Na_2PdCl_4 (0.1 mmol), $NaHCO_3$ (0.2 mmol), and EtOH (3 cm^3) was stirred in a 100 cm^3 stainless-steel pressure bottle at room temperature for 1 h to give a yellow suspension. Piperidine (0.05 cm^3) was then added. The heterogeneous mixture quickly turned pale yellow. After evacuating the system, CO gas (80 atm) was introduced and the mixture was stirred for 40 h at room temperature. The CO gas was purged and the resulting slightly yellow solution containing a black precipitate was analyzed by means of GLC and GC-mass spectrometry. The analysis revealed formation of α-keto amide **4a** (70%/Pd) together with negligible amounts of oxamide **5** and amide. The α-keto amide thus formed was isolated by a bulb-to-bulb distillation and characterized by means of IR and NMR spectroscopy.$^{11)}$

Double carbonylation of arylpalladium complexes **6a** and **6b**, prepared by orthopalladation reactions of acetanilide$^{12)}$ and N,N-dimethylbenzylamine,$^{13)}$ was examined in the presence of Et_2NH. The carbonylation reactions afford α-keto amides (**7a** and **7b**) in modest yields together with the corresponding amides and oxamide. The α-keto amide formation from **6a** and **6b** requires the presence of tertiary phosphine ligand. Thus, in the absence of phosphine, the reactions exclusively formed amides, the monocarbonylation products (Scheme 2).



Scheme 2.

In the carbonylation reactions of aroyl- and arylpalladium complexes affording α-keto amides, the palladium complexes are converted into Pd(0) species. If the resulting Pd(0) species can be converted into Pd(II) complexes by an appropriate oxidizing agent, a catalytic process converting aromatic aldehydes and hydrocarbons into α-keto amides is possible. As a preliminary attempt we examined carbonylation of **1a** and piperidine under 60 atm of CO in EtOH containing Na_2PdCl_4 (2 mol%/ **1a**) and $CuCl_2$ (1 equiv./ **1a**). The reaction gave unidentified compounds without formation of α-keto amide. Further attempts with various oxidizing agents including benzoquinone and copper halides are in progress.

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8) Use of Et_3N, NaOMe, or NaOCOMe in place of $NaHCO_3$ resulted in decomposition of the palladium complex.

9) **3a** Found: C, 48.77; H, 2.94; N, 7.43; Cl, 9.40%. Calcd for $C_{15}H_{11}ClN_2OPd$: C, 48.15; H, 2.90; N, 7.34; Cl, 9.43%.

10) **3b** Found: C, 45.55; H, 4.10; N, 7.59; Cl, 9.60%. Calcd for $C_{14}H_{15}ClN_2OPd$: C, 45.49; H, 3.95; N, 7.52; Cl, 9.43%.

11) **4a**: IR (KBr) 1680 and 1630 cm^{-1}; MS (70eV) 268 (M^+), 156 (base), 112.
4b: IR (KBr) 1660 and 1640 cm^{-1}; MS (70eV) 262 (M^++1), 261 (M^+), 156 (base), 112.

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