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CATALYTIC DOUBLE CARBONYLATION OF ORGANOHALOGEN COMPOUNDS PROMOTED BY PALLADIUM COMPLEXES

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Abstract: Various organohalogen compounds can be catalytically converted into α-keto amides on reaction with carbon monoxide and amines. Tertiary phosphine-coordinated palladium compounds are particularly suitable as the double carbonylation catalyst.

In contrast to the well-known mono-carbonylation reaction of organic compounds,[1)] the precedents of double carbonylation are extremely limited.[2)] Recently we found a stoichiometric double carbonylation of monoalkylpalladium complexes to proceed in the presence of secondary amines affording α-keto amides in good yields and selectivities under mild conditions.[3)]

$$\mathrm{RPd(X)L_2} \quad + \quad 2\mathrm{CO} \quad + \quad \mathrm{R'_2NH} \longrightarrow \mathrm{RCOCONR'_2} \qquad (1)$$

$$(\mathrm{R = Me,\ Ph;\ X = Br,\ I;\ L = PMePh_2,\ PPh_3;}\ \mathrm{R'_2NH = Et_2NH},\ \text{morpholine, piperidine})$$

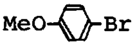
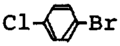
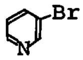
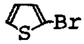
We now report the catalytic conversion of organic halides (RX), CO and amines (R'_2NH) into α-keto amides promoted by palladium compounds as realized by simple extension of the stoichiometric reactions.

$$\mathrm{RX} \quad + \quad 2\mathrm{CO} \quad + \quad 2\mathrm{R'_2NH} \xrightarrow{[\text{catalyst}]} \mathrm{RCOCONR'_2} \quad + \quad \mathrm{R'_2NH_2X} \qquad (2)$$

α-Keto amides can be obtained using aryl halides in a selectivity of ca. 90% under appropriate conditions accompanied by amides, the monocarbonylation products. Organopalladium compounds PdR_2L_2, $PdR(X)L_2$ as well as $PdCl_2L_2$ can be employed as the catalysts and the reaction is applicable to various organic halides including aryl, aralkyl, and alkenyl halides, as shown in Tables 1 and 2.

Typical procedure is as follows: PhBr (1 ml, 9.6 mmol) and Et_2NH (3 ml, 29 mmol) were added to a 50 ml stainless-steel autoclave containing $PdCl_2(PMePh_2)_2$ (49 mg, 0.085 mmol) under nitrogen atmosphere. After evacuation, CO gas (10 atm at room temperature) was introduced to the system and the mixture was stirred at 100°C. After 40 h, $PhCOCONEt_2$(82%) and N,N-diethylbenzamide(13% yield; based on

Table 1. Double Carbonylation of Organic Halides in the Presence of Amines[a]

RX	R'$_2$NH	Reaction Temp. (°C)	Reaction Time (h)	Product Ratio RCOCONR'$_2$	Product Ratio RCONR'$_2$	Total[b] Yield(%)
PhBr	Et$_2$NH	100	40	0.86	0.14	95
PhBr	_n_-Pr$_2$NH	100	50	0.90	0.10	44
PhBr	_i_-Pr$_2$NH	100	50	0.00	1.00	3
PhBr	piperidine	100	64	0.31	0.69	62
PhBr	morpholine	100	47	0.21	0.79	42
PhCl	Et$_2$NH	100	46	—	trace	trace
PhI	Et$_2$NH	100	45	0.32	0.68	100
PhI[c]	Et$_2$NH	100	45	0.44	0.56	90
PhI	_n_-Pr$_2$NH	100	42	0.29	0.71	100
	Et$_2$NH	100	45	0.84	0.16	98
	Et$_2$NH	100	50	0.80	0.20	25
	Et$_2$NH	100	50	0.69[d]	0.31[e]	88
	Et$_2$NH	100	63	0.58	0.42	100
	Et$_2$NH	100	43	0.15	0.85	80
PhCH=CHBr[f]	Et$_2$NH	r.t.[g]	88	0.52[i]	0.48[j]	41
PhCH=CHBr[f]	Et$_2$NH	50[h]	46	0.12[i]	0.88[k]	43

a) Reactions were carried out in a 20 mmol scale using PdCl$_2$(PMePh$_2$)$_2$ as catalyst without solvent. RX/R'$_2$NH/Catalyst ≃ 1/3/0.01 (molar ratio). p(CO) = 10 atm measured at room temperature. b) Based on organic halides. Determined by GLC. c) Benzene (25 ml) was used as solvent. d) ClC$_6$H$_4$COCONEt$_2$ e) ClC$_6$H$_4$CONEt$_2$ f) _Cis_ (1) and _trans_ (6.5) mixture was used. g) PdMe$_2$(PMePh$_2$)$_2$ was used as catalyst. h) PdCl$_2$(PEt$_2$Ph)$_2$ was used as catalyst. i) _Trans_ isomer was formed selectively. j) _Cis_ (1) and _trans_ (6.5) mixture. k) _Cis_ (1) and _trans_ (39) mixture.

PhBr) were obtained as confirmed by means of GLC. Identification of these reaction products was performed by means of IR and NMR spectroscopy, and mass spectrometry after isolation of the products.

The selectivity of the double carbonylation is higher with the bromides than with the iodides. The reaction rates are lower when the chlorides are employed. Basic and less bulky amines seem to be suitable for the double carbonylation reaction. Although nonpolar solvents were found to be effective for increasing the double carbonylation products in the stoichiometric double carbonylation,[3] benzene was not so effective solvent in the catalytic system. Organic halides reacting

Table 2. Catalytic Activity of Various Transition Metal Complexes on the Double Carbonylation of PhBr in the Presence of Et_2NH[a)]

Catalyst[b)]	Reaction Temp. (°C)	Reaction Time (h)	Product Ratio		Total[c)] Yield (%)
			$PhCOCONEt_2$	$PhCONEt_2$	
$PdPh(Br)(PPh_3)_2$	100	35	0.47	0.53	87
$PdPh(Br)(PMePh_2)_2$	100	35	0.80	0.20	70
$PdPh(Br)(PMePh_2)_2$	80	28	0.86	0.14	62
$PdCl_2(PMePh_2)_2$	100	40	0.86	0.14	95
$PdCl_2(PEt_2Ph)_2$	100	42	0.84	0.16	50
$PdCl_2(PMe_2Ph)_2$	100	42	0.89	0.11	19
$PdCl_2(PEt_3)_2$	100	42	0.77	0.23	9
$PdCl_2(dpe)$	100	40	0.49	0.51	100
$PdCl_2$	100	43	—	—	0
$Pd(OAc)_2$	100	43	—	—	0
$PdCl_2(bpy)$	100	43	—	—	0
$CuBr(PPh_3)_3$	100	40	0.58	0.42	0.8[d)]
$NiCl_2(PEt_3)_2$	100	40	0.00	1.00	1.3[e)]
$RhCl(PPh_3)_3$	100	70	—	—	0
$CoCl(PPh_3)_3$	100	70	0.29	0.71	10
$CoCl_2(PEtPh_2)_2$	100	61	—	—	0

a) Carried out in a 20 mmol scale without solvent. $PhBr/Et_2NH/Cata. \simeq 1/3/0.01$ (molar ratio). p(CO) = 10 atm at room temperature.

b) dpe = $Ph_2PCH_2CH_2PPh_2$. bpy = 2,2'-bipyridine.

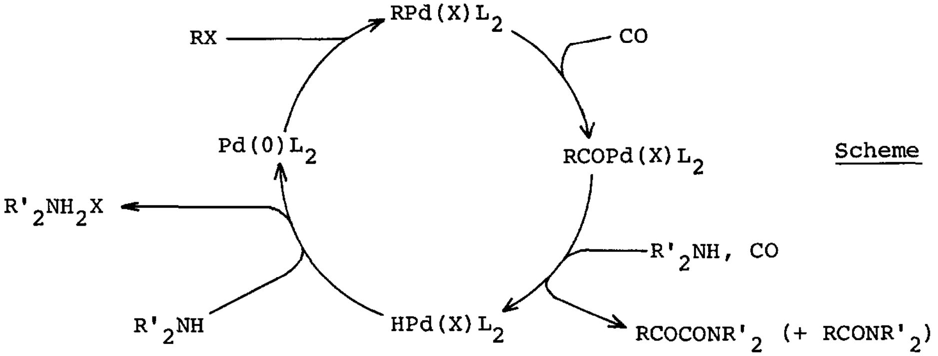
c) Based on PhBr. Determined by GLC.

d) 100%/Cu. e) 73%/Ni.

with amines are usually not suitable for the reaction, although benzyl chloride did produce $PhCH_2COCONEt_2$ in a low yield (3%) together with $PhCH_2NEt_2$ which was formed as the main reaction product. The reactions are applicable to halides of heterocycles as well as to halostyrenes.

Among other catalysts examined, $CoCl(PPh_3)_3$ was mildly active affording α-keto amides in the selectivity of 29% while $NiCl_2(PEt_3)_2$, $CoCl_2(PEtPh_2)_2$, and $RhCl(PPh_3)_3$ were inactive. Stoichiometric conversion of PhBr to $PhCOCONEt_2$ promoted by $CuBr(PPh_3)_3$ was found to proceed in the yield of 58%/Cu.

The overall catalytic reactions may proceed as shown in the following scheme, which involves oxidative addition of organic halides to Pd(0) compounds to give $RPd(X)L_2$ followed by CO insertion into Pd-C bond to afford an acylpalladium species.



Scheme

As established in the stoichiometric reaction (eq. 1), the reaction of alkyl- or arylpalladium halide complexes with CO in the presence of the amine leads to α-keto amides together with some amides.

Whether the double carbonylation proceeds by a double CO insertion into a Pd-C bond giving RCOCO-Pd species to be trapped by amine or by a single CO insertion giving a CO-coordinated acylpalladium species RCO-Pd(CO) followed by the attack of amine on the coordinated CO to give an acyl-carbamoyl species $RCO\text{-}Pd\text{-}CONR'_2$, which reductively eliminates $RCOCONR'_2$, is presently undecided.

Since the reaction route from α-keto acid derivatives to α-amino acids through imine derivatives is well established,[4)] the present reaction promises to afford a generally applicable route for synthesis of a variety of α-amino acids.

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