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PALLADIUM-CATALYZED DOUBLE CARBONYLATION REACTIONS OF ARYL HALIDES AFFORDING α-KETO ESTERS

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Various aryl iodides can be converted into α-keto esters in reactions with carbon monoxide and alcohols in the presence of tertiary amines and catalytic amounts of tertiary phosphine-coordinated palladium complexes.

The recently found palladium-catalyzed double carbonylation reaction, which converts organic halides, amines, and carbon monoxide into α-keto amides, provides a convenient means for introducing two reactive carbonyl groups in one step into an organic compound.$^{1,2)}$ The utility of this process, however, is somewhat limited when the α-keto amides obtained are resistant to hydrolysis. Thus it is desirable to perform the double carbonylation using alcohol to give α-keto esters. We now report that such double carbonylation can be achieved with aryl iodides under CO pressure.$^{3)}$

Reactions of aryl iodides with alcohols under CO pressure give corresponding α-keto esters together with esters, the single carbonylation by-products. Presence of a catalytic amount of palladium complex and a base such as triethylamine, which serves as a reagent to remove hydrogen iodide generated in the reaction, is an essential requirement for the reaction to proceed.

$$\mathrm{ArI + 2CO + ROH + Base \xrightarrow{Pd\text{-}catalyst} ArCOCOOR + ArCOOR + Base{\cdot}HI} \qquad (1)$$

Table 1 summarizes the results of the reactions of phenyl iodide under various conditions. Among tertiary phosphines examined as ligand, the basic and bulky tricyclohexylphosphine gave the best results in yielding α-keto ester in high selectivity. Diphenylmethylphosphine and 1,4-bis(diphenylphosphino)butane, which gave best results for production of α-keto amides, are less effective for the synthesis of α-keto esters. Sterically demanding secondary alcohols such as 2-butanol, 2-octanol, and 4-heptanol are suitable for α-keto ester formation (runs 1-5). Raising the temperature accelerates the reaction but lowers the selectivity for double carbonylation (runs 3 and 6-8). Under higher CO pressure the reaction proceeds more rapidly, although the selectivity for double carbonylation is somewhat lowered (runs 7 and 9-12).

Considerable solvent effect on the selectivity for α-keto ester formation was observed (Table 2). The reactions carried out in less polar solvents such as

Table 1. Double Carbonylation of Phenyl Iodide in the Presence of Alcohols under Various Conditions[a)]

Run	Catalyst[b)]	Alcohols	CO[c)] (atm)	Reaction temp / °C	Reaction time / h	Selectivity/ %		Conversion of PhI/ %
						PhCOCOOR	PhCOOR	
1	$PdCl_2(PCy_3)_2$	MeOH	70	70	92	3	97	100
2	$PdCl_2(PCy_3)_2$	EtOH	70	70	92	17	83	97
3	$PdCl_2(PCy_3)_2$	2-Butanol	70	70	96	66	34	74
4	$PdCl_2(PCy_3)_2$	2-Octanol	70	70	119	64	36	91
5	$PdCl_2(PCy_3)_2$	4-Heptanol	60	70	48	76	24	35
6	$PdCl_2(PCy_3)_2$	2-Butanol	70	60	48	77	23	37
7	$PdCl_2(PCy_3)_2$	2-Butanol	70	80	48	60	40	60
8	$PdCl_2(PCy_3)_2$	2-Butanol	70	100	48	21	79	96
9	$PdCl_2(PCy_3)_2$	2-Butanol	20	80	48	60	40	10
10	$PdCl_2(PCy_3)_2$	2-Butanol	40	80	48	57	43	36
11	$PdCl_2(PCy_3)_2$	2-Butanol	80	80	48	47	53	82
12	$PdCl_2(PCy_3)_2$	2-Butanol	90	80	48	35	65	93
13	$PdCl_2(PMePh_2)_2$	2-Butanol	70	80	48	13	87	86
14	$PdCl_2(dppb)$	2-Butanol	70	80	48	15	85	85

a) Reactions were carried out using PhI (5 mmol), alcohol (7.6 - 11 mmol), Et_3N (7.6 mmol), and catalyst (0.1 mmol) in CH_2Cl_2 (1.5 - 2 cm^3). b) PCy_3 = tricyclohexylphosphine. dppb = $Ph_2P(CH_2)_4PPh_2$. c) Initial pressure measured at room temperature. (1 atm = 101325 Pa).

dichloromethane and benzene afford α-keto esters in high selectivity, whereas addition of polar solvents such as acetone and N,N-dimethylformamide to the system decreases the selectivity. The double carbonylation reaction is markedly affected by base. Among bases examined, triethylamine was found to be the most suitable for double carbonylation.

By taking above information into account, α-keto ester synthesis from several kinds of aryl iodides was examined. The results are listed in Table 3. The present double carbonylation reaction is applicable to iodides of aromatic heterocycles as well as substituted phenyl iodides. The process is also applicable to aryl bromides, although the reactions of bromides are much slower than those of iodides.

As compared with the double carbonylation affording α-keto amides the present reaction producing α-keto esters requires more severe reaction conditions and longer reaction time. In the previous mechanistic studies on the α-keto amide formation reaction we demonstrated that nucleophilic attack of amine on the

Table 2. Effects of Solvent and Base on the Double Carbonylation of Phenyl Iodide and 2-Butanol Catalyzed by PdCl$_2$(PCy$_3$)$_2$ a)

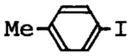
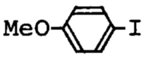
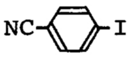
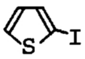
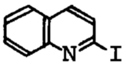
Run	Base c)	Solvent	CO d) (atm)	Reaction temp / °C	Reaction time / h	Selectivity / %		Conversion of PhI / %
						PhCOCOOR	PhCOOR	
1	Et$_3$N	Benzene	70	80	48	51	49	40
2	Et$_3$N	Benzene	70	70	119	63	37	97
3	Et$_3$N	CH$_2$Cl$_2$	70	80	48	60	40	60
4	Et$_3$N	CHCl$_3$	70	80	48	50	50	72
5	Et$_3$N	PhCl	70	80	48	53	47	38
6	Et$_3$N	THF	70	80	48	38	62	48
7	Et$_3$N	Acetone	70	80	48	33	67	36
8	Et$_3$N	DMF	70	80	48	12	88	100
9	Et$_3$N	—— b)	70	80	43	24	76	100
10	DBU	CH$_2$Cl$_2$	70	80	48	10	90	91
11	NPh$_3$	CH$_2$Cl$_2$	70	80	48	0	100	6
12	*i*-Bu$_3$N	CH$_2$Cl$_2$	70	80	48	0	100	16
13	Pyridine	CH$_2$Cl$_2$	70	80	48	0	100	12
14	2-BuONa	—— b)	70	80	48	7	93	19

a) Reactions were carried out using PhI (5 mmol), 2-butanol (11 mmol except for runs 9 and 14, 16 mmol), base (≈7.6 mmol), and PdCl$_2$(PCy$_3$)$_2$ catalyst (0.1 mmol) in solvent (2 cm^3 except for runs 9 and 14). b) Reactions were carried out without solvent. c) DBU = 1,8-diazabicyclo[5.4.0]-7-undecene. d) Initial pressure measured at room temperature.

coordinated CO ligand constitutes a key step regarding the rate and selectivity.4) The lower rate in the present system may be attributable to the lower nucleophilicities of alcohols than those of secondary amines. Detailed mechanistic studies regarding the factors governing the selectivity for α-keto ester formation will be reported later.

Typical procedure is as follows: PhI (1.0 g, 5 mmol), 2-butanol (1.1 cm^3, 11 mmol), Et$_3$N (1.1 cm^3, 7.6 mmol), and benzene (2 cm^3) were added to a 100 cm^3 stainless-steel autoclave containing PdCl$_2$(PCy$_3$)$_2$ (0.074 g, 0.1 mmol) under nitrogen atmosphere. CO gas (70 atm at room temperature) was introduced to the system and the mixture was magnetically stirred at 70 °C. After 119 h, 2-butyl benzoylformate (61%) and 2-butyl benzoate (35%; based on PhI) were obtained as confirmed by means of GLC. Identification of these products was performed by means of IR and ^{1}H NMR spectroscopy and mass spectrometry after isolation of the products by means of column chromatography.

Table 3. Double Carbonylation of Aryl Iodides and 2-Butanol Catalyzed by $PdCl_2(PCy_3)_2$ in CH_2Cl_2 a)

Run	ArI	CO b) (atm)	Reaction temp / °C	Reaction time / h	Selectivity / %		Conversion of ArI / %
					ArCOCOOR	ArCOOR	
1		70	70	72	69	31	82
2		70	70	72	63	37	75
3		70	70	72	48	52	97
4		70	70	96	64	36	95
5		70	70	72	22	78	100

a) Reactions were carried out using aryl iodide (≈5 mmol), 2-butanol (11 mmol), Et_3N (7.6 mmol), and $PdCl_2(PCy_3)_2$ catalyst (0.1 mmol) in CH_2Cl_2 (2 cm^3).

b) Initial pressure measured at room temperature.

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3) Very recently, a patent dealing with the similar process was disclosed; H. Itatani, S. Dan-no, and K. Zushi, Japan Kokai Tokkyo koho, JP 60-19750 (1985).

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