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Preliminary communication

PALLADIUM(II)-CATALYZED DOUBLE CARBONYLATION OF ORGANIC HALIDES IN THE PRESENCE OF AMINES: α-KETOAMIDE SYNTHESIS

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Summary

Aryl, hetero-aryl, and vinylic halides react with carbon monoxide (40 atm pressure or less) and a secondary amine at 60—100°C in the presence of a catalytic amount of palladium compound to form α-ketoamides, in addition to simple amides as by-products. When a primary amine was used in place of a secondary one, an imine of the α-ketoamide was readily obtained.

In spite of extensive investigation of palladium complex-catalyzed carbonylation of organic halides for the synthesis of acids, esters, amides, aldehydes and ketone derivatives [1], double carbonylation is not known. We recently reported amide formation through C—N bond fission of tertiary amines under Pd^{II}-catalyzed carbonylation conditions [2]. In the course of this study, we found a novel double carbonylation which gives α-ketoamides in good yield.

$$RX + CO + HNR'_2 \xrightarrow{Pd^{II}} RCOCONR'_2\ (+\ RCONR'_2)$$

A typical procedure for the reaction is as follows. In a 27 ml stainless steel autoclave, iodobenzene (4.0 mmol), diethylamine (3 ml, 29.8 mmol, as reactant, hydrogen halide scavenger and solvent), and dichloro[1,4-bis(diphenylphosphino)butane]palladium (1.88×10^{-2} mmol) were placed under a nitrogen atmosphere. The vessel was charged with carbon monoxide (40 atm at room temperature), and heated in an oil bath at 60°C till the gas absorption ceased. After 4 h, the vessel was cooled and the reaction mixture was analyzed by GLC, which showed that *N,N*-diethyl-2-phenylglyoxylamide had been formed in 98.1% yield along with *N,N*-diethylbenzamide in 1.6% yield. After filtration of the ammonium salt, the filtrate was distilled to give the pure glyoxylamide in 94.4% yield (b.p. 110°C/0.1 Torr, Kugelrohr distillation apparatus, lit. [3] b.p. 116°C/0.1 Torr).

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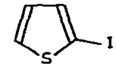
In a separate experiment, *N*,*N*-diethylbenzamide in place of iodobenzene was allowed to react with carbon monoxide in the presence of diethylamine and the palladium catalyst under the same conditions as those described above. However, carbon monoxide was not absorbed, and the starting material was recovered unchanged. This result clearly indicates that the α-ketoamide was not formed in a stepwise manner via the carbonylation of the benzamide once formed in situ, but was formed as the initial product via the double carbonylation.

The results for other combinations of halides and amines are listed in Table 1. As shown in the table, the double carbonylation also occurred for heteroaromatic and vinylic halides, although the selectivity to α-ketoamides (versus simple amides via monocarbonylation) was not so high. The choice of secondary amines played a decisive role for the selective α-ketoamide synthesis from iodobenzene (entries 6, 21—23). Thus, diethylamine and dipropylamine gave the corresponding α-ketoamides in good yields, while dimethylamine caused extensive mono-carbonylation to give the benzamide as the main product. In the case of diisopropylamine, double carbonylation did not occur at all.

TABLE 1

α-KETOAMIDE SYNTHESIS THROUGH CARBONYLATION OF ORGANIC HALIDES IN THE PRESENCE OF AMINES[a]

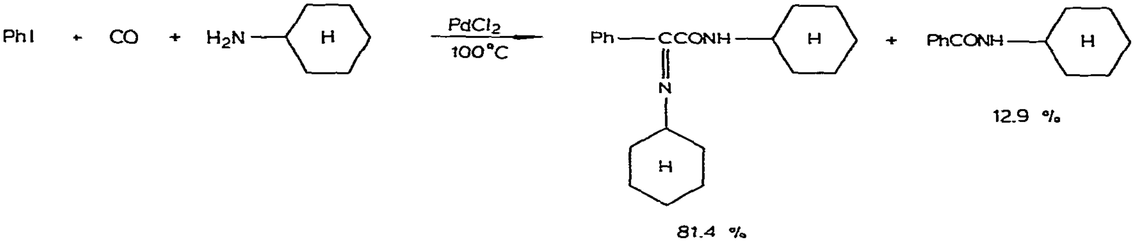
Entry	RX	HNR'_2	Catalyst	Temp.[b] (°C)	p(CO) (atm)	Reaction time (h)	Product yield (%)[c]	
							$RCOCONR'_2$	$RCONR'_2$
1	PhI	$HNEt_2$	$PhPdI(Ph_3P)_2$	60	40	2	71.5	24.1
2	PhI	$HNEt_2$	$PdCl_2(Ph_2EtP)_2$	60	40	5	73.8	22.4
3	PhI	$HNEt_2$	$PdCl_2(PhMe_2P)_2$	60	40	67	80.7	7.3
4	PhI	$HNEt_2$	$PdCl_2$(dppe)[d]	60	40	24	65.9	24.3
5	PhI	$HNEt_2$	$PdCl_2$(dppp)[e]	60	40	19	87.3	6.0
6	PhI	$HNEt_2$	$PdCl_2$(dppb)[f]	60	40	4	98.1 (94.4)	1.6
7	PhI	$HNEt_2$	$PdCl_2$(dppt)[g]	60	40	4	79.9	14.3
8	PhI	$HNEt_2$	$PdCl_2$(DIOP)	60	40	4	87.9	7.4
9	PhI	$HNEt_2$	$PdCl_2$	60	20	84	80.5	9.6
10	PhI	$HNEt_2$	$PdCl_2$	100	20	4	85.5	12.2
11	PhI	$HNEt_2$	Pd/C	100	20	3	83.3	14.0
12	PhI	$HNEt_2$	PdO	100	20	2	83.5	13.6
13	PhI	$HNEt_2$	Pd-black	100	20	22	85.7	13.0
14	PhI	$HNEt_2$	$PdCl_2(PhCN)_2$	100	20	3.5	84.5	12.8
15	PhI	$HNEt_2$	$PdCl_2$(dppb)	60	20	5	96.5	2.5
16	PhI	$HNEt_2$	$PdCl_2$(dppb)	60	8	7	91.4	6.3
17	PhI	$HNEt_2$	$PdCl_2$(dppb)	60	1	32[h]	9.6	24.1
18	PhI	$HNEt_2$	$PdCl_2$(dppb)	100	40	2	88.8	10.8
19	PhI	$HNEt_2$	$PdCl_2$(dppb)	100	20	3	75.6	22.8
20	PhI	$HNEt_2$	$PdCl_2$(dppb)	100	8	6	37.8	59.9
21	PhI	$HNMe_2$	$PhPdI(Ph_3P)_2$	60	40	3	9.7	80.3
22	PhI	$HNPr_2$	$PhPdI(Ph_3P)_2$	60	40	3	81.4 (75.1)	13.8
23	PhI	HN(i-Pr)$_2$	$PhPdI(Ph_3P)_2$	120	25	4	0	92.0
24	PhBr	$HNEt_2$	$PdCl_2$(dppb)	100	20	48	73.9	9.7
25		$HNEt_2$	$PdCl_2$(dppb)	60	40	4	66.1	28.6
26	PhCH=CHBr	$HNEt_2$	$PdCl_2$(dppb)	60	40	6	54.4 (51.0)	45.3

[a] Halide 4.0 mmol, amine 3 ml, catalyst 1.88 $\times 10^{-2}$ mmol. [b] Oil bath temperature. [c] The figures in parentheses are isolated yields. [d] 1,2-bis(diphenylphosphino)ethane. [e] 1,3-bis(diphenylphosphino)propane. [f] 1,4-bis(diphenylphosphino)butane. [g] 1,5-bis(diphenylphosphino) pentane. [h] Recovered PhI was 64.6%.

In order to improve the selectivity to the α-ketoamide, the effect of the structure of the catalyst and that of the reaction conditions were examined for the combination of iodobenzene and diethylamine. These results are also listed in Table 1. As Table 1 shows, $PdCl_2(dppb)$ (for abbreviations, see the footnotes of Table 1) was the best catalyst. It is interesting that the selectivity to α-ketoamide exhibited by bidentate phosphine-palladium complex catalyst is dependent on the length of the carbon chain and the framework between the two diphenylphosphino groups; the order of the selectivity was dppb $>$ dppp $\gtrsim$ diop $>$ dppt $>$ dppe (entries 4—8). Palladium chloride, palladium on carbon, palladium oxide, palladium black, and dichlorobis(benzonitrile)palladium were also effective for the selective α-ketoamide synthesis from iodobenzene (entries 9—14). Among monodentate phosphine complexes of palladium, the more basic phosphines seem to exhibit better selectivities (entries 1—3).

Although the reaction could be effected under atmospheric pressure of carbon monoxide, extensive benzamide formation resulted. For a high selectivity to the α-ketoamide, the reaction should be run under elevated pressures (entries 6, 15—17 and entries 18—20). With regard to the effect of the reaction temperature on the selectivity, lower temperature was more favorable for the α-ketoamide formation (compare entries 6, 15, and 16 with 18, 19, 20, respectively).

In addition to these results, double carbonylation occurred also for the reaction with a primary amine. For example, when cyclohexylamine was used in place of a secondary amine, the main product was the imine of the α-ketoamide, as shown below.



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